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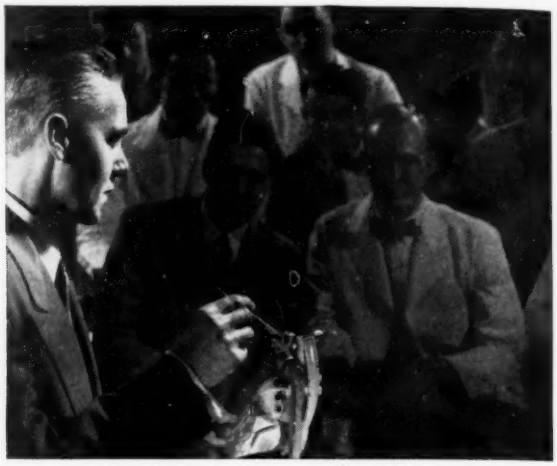

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TABLE *of* CONTENTS

SPECIAL ARTICLES

I. Effect of Adrenals in Allergy. II. Effect of Cortisone in Clinical Allergy
LEO H. CRIEP, M.D. 383

The Role of Surgery in Peptic Ulcer
ALEC HORWITZ, M.D. 391

Toxemia of Pregnancy; Outline of Treatment
STANLEY T. GARBER, M.D. 402

Misconceptions Leading to Delay in the Diagnosis of Intracranial Space-Taking Lesions
WILLIAM R. CHAMBERS, M.D. 405

Fallacy in Allergy
ASHER A. WHITE, M.D. 410

A New Approach to Increasing Tolerance to Oral Aminophylline
GEORG CRONHEIM, M.D., T. T. JUSTICE, JR., M.D. AND J. STANTON KING, JR., M.D. 432

John Arderne, the Father of English Surgery
GERALD N. WEISS, M.D. 479

DIAGNOSTIC CLINICS

Neurosurgical Clinic
W. JAMES GARDNER, M.D. 417

Papilloma of the Bladder
WILLIAM J. ENGEL, M.D. 423

Surgery in Poliomyelitis in Infancy and Childhood
WILLIAM T. MUSTARD, M.D. 428

CASE REPORT

Trilobectomy and Lingulectomy for Bronchiectasis
WILLIAM P. KLEITSCH, M.D. 435

CLINICAL STUDY

Clinical Experience with Tryptar in Treatment of Infected Wounds
JOSEPH M. MILLER, M.D., BEVERLY H. WHITE, M.D. AND PERRIN H. LONG, M.D. 438

(Continued on page A-6)

SCIENTIFIC EXHIBIT

Medical Illustration
THE BIOLOGICAL PHOTOGRAPHIC ASSOCIATION 443

GENERAL PRACTICE REVIEW

Hepatic Cirrhosis and Its Complications
CLARENCE W. LEGERTON, JR., M.D. 449
Pregnancy and Labor in the Cardiac Patient
RALPH A. REIS, M.D. 454
Myocardial Infarction—An Evolutionary Process
WINGATE M. JOHNSON, M.D. 459

PEDIATRICS IN GENERAL PRACTICE

Use of Mineral-Enriched Meats as a Substitute for Milk in Various Clinical Conditions
MILDRED R. ZIEGLER, PH.D. 461
Significance of Hepatomegaly in Infants and Children
GEORGE B. LOGAN, M.D. 469

DEPARTMENTS

EDITORIALS 473

The Nonsurgical Prolongation of Life
Decline of Mortality from Rheumatic Fever
Trauma and the Hand
Prognosis in Myocardial Infarction
University of Illinois Strengthens Rural Medical Practice
Chancroid
Skin Cleaners
The Green Wave of Chlorophyll Ebbs

POSTGRADUATE CLINICAL NOTES 404
6. *Leg Cramps in Pregnancy*

LETTERS FROM ABROAD A-12

THE MEDICAL MUSE. Richard Armour A-14

YOUR QUESTIONS ANSWERED A-28

Electrolysis
Remedies for Motion Sickness
Viral Hepatitis
Blood Donors

PORTRAITS AND PERSONALITIES. *Edward J. McCormick, M.D.* A-36

THE MEDICAL BOOKMAN A-54

NEW DRUGS AND INSTRUMENTS A-71

DR. PEPYS' PAGES. Morris Fishbein, M.D. A-76

INDEX TO TECHNICAL EXHIBITS A-112

I. Effect of Adrenals in Allergy
II. Effect of Cortisone in Clinical Allergy

LEO H. CRIEP*

University of Pittsburgh School of Medicine, Pittsburgh

This paper includes a summary of the present knowledge of and the author's clinical experience with corticosteroids in allergy. It covers indications, precautions, dosage and contraindications in therapy.

LEO H. CRIEP

We have shown previously[1] that the adrenal cortex plays an important role in certain phases of experimental allergy. Extirpation of the adrenals enhances the precipitin titer, the Arthus phenomenon and anaphylactic shock. It also increases the severity and extent of the lesions of experimental diffuse arteritis (collagen disease). These effects are probably brought about through the resulting compensatory hypertrophy of the lymph glands. Administration of cortisone in the adrenalectomized animal does not affect these phenomena.[2,3] Administration of cortisone in the intact animal in our hands[4] does not seriously affect the precipitin reaction, the Arthus phenomenon or the anaphylactic reaction. It does seem to reduce the extent and severity of experimental collagen disease. These relatively weak effects of cortisone in experimental allergy are in marked contrast to the well known and often dramatic effects observed following the administration of ACTH and cortisone in both the immediate and some delayed types of clinical allergic conditions. There are many detailed reports indicating the effectiveness of such therapy in individual allergic conditions. This paper is a summary of the present knowledge of the subject including a short review of adrenocortical physiology; the physiologic and metabolic effects of the corticosteroids; precautions to be employed prior to and during such therapy; procedures adopted to avoid side effects; dosage and forms in which these products are now available; contraindications, and, finally, a critical summary of our own experiences with the use of ACTH and cortisone in a large series of allergic diseases during the past two years.

Adrenocortical Physiology

ACTH is produced by the anterior pituitary gland in response to stimulation by the hypothalamus (Figure 1). The hypothalamus in turn is stimulated by epinephrine, the secretory product of the adrenal medulla. ACTH is a protein. It stimulates the adrenal cortex to secrete hormones. These biologically active hormones (adrenal corticoids) are steroids. Many different steroids, about 28 in all, have been separated from the adrenal cortex.[5] Of

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Cortisone was supplied by Merck and Company.

Through a grant by the Lasden Foundation, Nepera Park, New York.

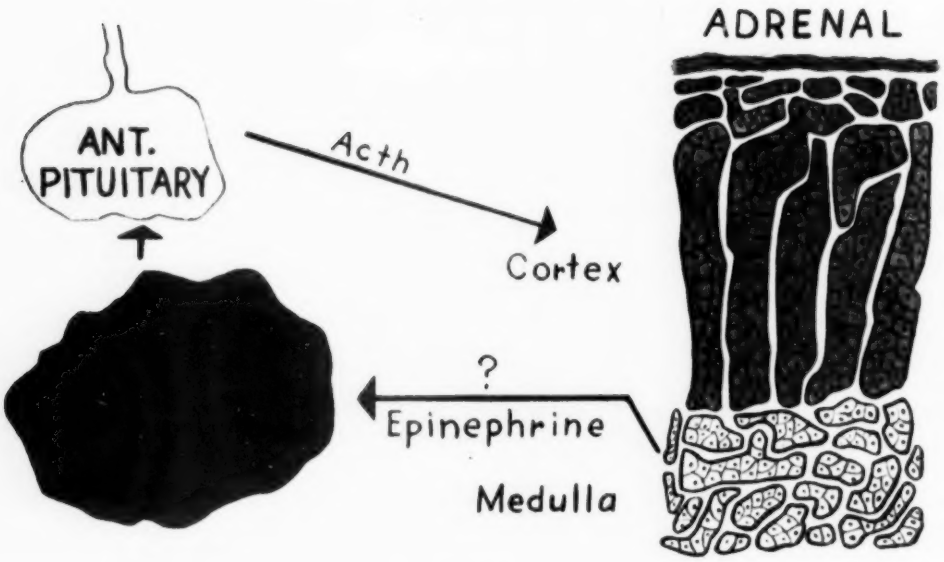

FIGURE 1

these, about six have been shown to be biologically active. These fall into three types (Figures 2 and 3):

1. 11-desoxycorticosterone—This hormone has powerful effects in controlling salt and electrolyte metabolism. Actually, it is not known definitely whether it is produced normally by the adrenal cortex. There is some evidence to indicate that another steroid similar in biologic effect to 11-desoxycorticosterone, namely, corticosterone or compound B, is secreted by the adrenal cortex. Another similar type of steroid is 11-desoxy, 17-hydroxycorticosterone.

2. Androgenic steroids (adrenosterone)—These hormones effect a sex function and also bring about positive nitrogen balance.

3. Compound F-like hormones—These include compound F or 17-hydroxycorticosterone (hydrocortisone) and compound E (17-hydroxy, 11-dehydrocorticosterone or cortisone. Compound F or hydrocortisone is one of the main hormones secreted by the adrenal cortex in man. Whether the other steroids are secreted by the human adrenal cortex and, if so, to what extent, remains to be determined.[6-12] It is this type of biologically active hormone that is chiefly concerned with carbohydrate metabolism; its physiologic and metabolic effects render it important in a discussion of the subjects of the immunology and allergy.

Since ACTH stimulates the adrenal cortex, it follows that its administration produces metabolic and therapeutic effects similar to that produced by compound F and cortisone. It may be said, then, that in addition to its sex function the adrenal cortex controls electrolyte and water metabolism as well as the metabolism of carbohydrates, protein and fat.

Physiologic and Metabolic Effects

The physiologic and metabolic effects of ACTH and adrenal corticosteroids may be divided into early, late and miscellaneous effects.

The early effects are:

1. Hyperglycemia and glycosuria, indicating the need of caution in the use of the hormones in the presence of diabetes mellitus.

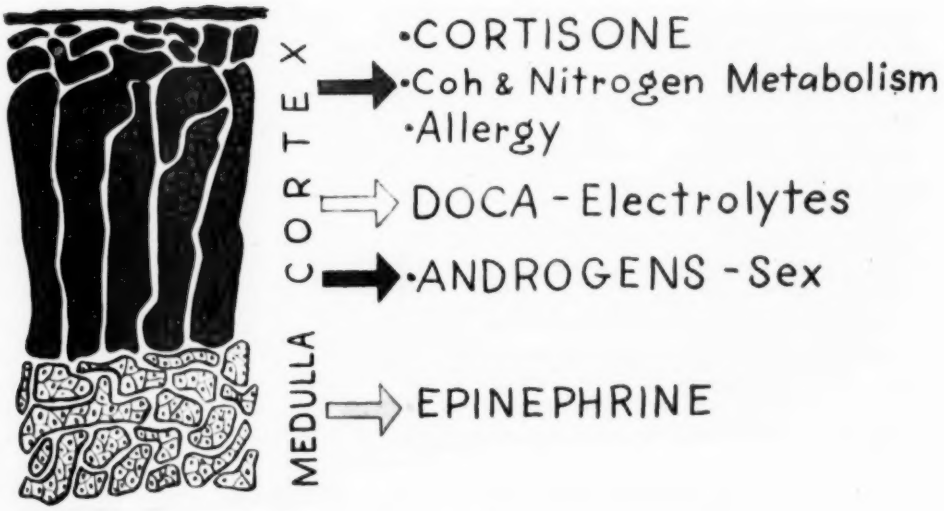

FIGURE 2

2. Retention of sodium and water resulting in edema and an increase in weight.

3. Hypopotassemia which is brought about as a result of excessive potassium excretion, as well as because of storage in the liver with glycogen. There is a diminution of intracellular and extracellular potassium. Cardiac function may then be impaired. The condition may be recognized by serum potassium determinations or by the characteristic electrocardiographic changes—a prolonged QT and P-R interval with inversion of T waves.[13]

4. Lymphopenia and eosinopenia. As is well known, there is a drop in the circulating eosinophil count after the administration of these hormones. As a rule, if no drop occurs after ACTH administration, one may conclude that the adrenal cortex is not responsive and that therefore the injection of ACTH will be ineffective.

5. Increased protein catabolism and therefore negative protein balance.

6. Hypochloremia and alkalosis. This may occur especially if mercurial diuretics are given to promote water excretion. Under these circumstances, great loss of chlorides

SIX BIOLOGICALLY ACTIVE STEROIDS FROM ADRENAL CORTICAL TISSUE

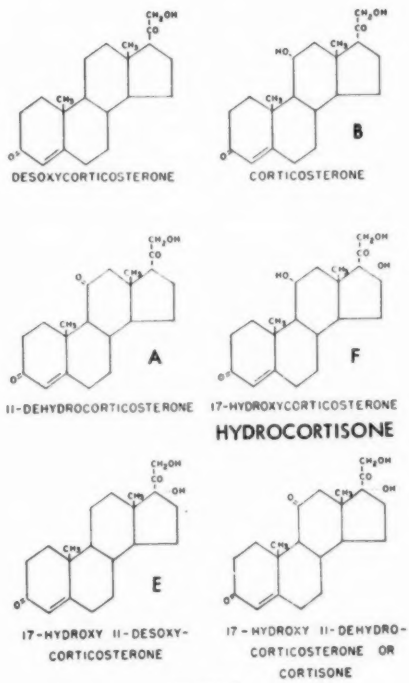

FIGURE 3

leads to hypochloremia and an excess bicarbonate so that alkalosis results.

Late effects:

1. Cushing syndrome: hirsutism, acne, hypertension, moon face and polycythemia.

2. Menstrual disturbances.

Miscellaneous effects:

1. Psychogenic changes. These may include euphoria, depression and convulsions. There is evidence of cerebral cortical activity brought about by these hormones. Muscle strength returns. Sleeplessness may be produced. Increased mental activity is especially pronounced in individuals with a neurotic or psychopathic personality and early it may be accompanied by lack of power to concentrate and by a state of depression. These constitute a warning to discontinue hormone therapy.

2. Effects on enzyme systems. There is evidence that many enzyme systems are affected by ACTH and cortisone. Those of special interest are hyaluronidase and histaminase. Hyaluronidase is an enzyme which aids in the spreading factor. This is done by breaking down the hyaluronic acid in the connective tissue. Dyes injected locally may be shown to spread further if hyaluronidase is also introduced. However, if cortisone is added to the hyaluronidase, then the spreading factor is inhibited or reduced. This may have some significance when we come to explain the inhibiting action of cortisone in certain allergic diseases.[14,15] The probable rise in histaminase level following ACTH and cortisone therapy may also be significant in interpreting the possible mechanism of action of these hormones in allergic diseases since histaminase is supposed to neutralize histamine—the product of antigen-antibody union. It would also appear that the local formation of histamine is reduced. These hormones apparently inhibit the formation of histamine from histidine. Furthermore, decreased histamine also results from excessive excretion of histidine.

Procedures and Precautions to Be Followed in the Use of ACTH and Cortisone

In light of what has been said about the various metabolic and physiologic effects of these steroids it follows that such therapy should not be instituted on an ambulatory basis. Treatment should always be preceded by an initial period of study and observation. This should include an opportunity to meet promptly any indications of undesirable complications. Following are the procedures to be employed in preparation for or during hormone therapy:

1. Thorn test.[16] This is employed by many clinicians. It determines whether the adrenal cortex is responsive to ACTH therapy. The test consists in the determination of the eosinophil count following a preliminary injection of ACTH. A fall in the eosinophil count indicates a good adrenal response. If such response is absent, there is no point in administering ACTH. Cortisone is then given. There are, however, some instances in which a second course of ACTH may prove therapeutically ineffective even in the presence of a normal, responsive adrenal cortex. This may be due to the presence of antibodies or antihormones which were produced as a result of the first course of ACTH therapy (especially if hypothyroidism is present).

2. Fluid intake and output record is an indication of water retention. The weight record also helps determine water retention.

3. Blood pressure rise is a signal of untoward reaction.

4. Urine and blood sugar rise constitutes a complication.

5. Potassium serum level may fall and sodium serum level may rise.

6. The electrocardiogram is a readily available index of hypopotassemia.

7. Blood chloride changes may be an early indication of impending alkalosis.

If any danger signals occur, or in order to help in their prevention, it is well to:

1. Prescribe a low sodium diet (less than 0.5 gm. of sodium).

2. Discontinue mercurial diuretics if hypopotassemia or alkalosis is suspected.

3. Reduce the dose of the hormone if any side effects occur.

4. Administer potassium lactate or chloride, 3 to 6 gm. daily in enteric-coated tablets by mouth. These drugs may be given intrave-

nously (20 mEq. of potassium chloride to 1000 cc. 5 per cent glucose) if not tolerated by mouth. This should be done cautiously because hyperpotassemia and cardiac arrest may follow.

5. Increase protein intake in order to overcome the negative nitrogen balance induced as a result of steroid therapy.

6. Alternate ACTH and cortisone therapy in instances of prolonged therapy.

Dosage and Available Forms of ACTH and Cortisone

Both ACTH and cortisone are easily destroyed in the body. When injected intramuscularly, they are rendered, at least in part, ineffective by tissue enzymes. The dosage varies directly with the severity of the clinical condition. As the manifestations subside, the dose is also diminished. In a general way, the minimum effective dose should be employed. One must guard for obvious reasons against unnecessarily large doses. Furthermore, when it is desired to terminate therapy, this should be accomplished by a gradual tapering off in order to avoid adrenal crisis. Under normal conditions, the pituitary secretes ACTH which in turn stimulates the adrenal cortex to secrete compound F-like steroids. Unlimited secretion of ACTH is controlled by the inhibiting action of compound F-like steroids on the pituitary.

If ACTH is administered in large doses for a sufficiently long time there may develop a serious inhibition of secretion of endogenous ACTH as a result of the effect on the pituitary of the adrenal steroids secreted by such stimulation. At a time such as this, if the ACTH is suddenly discontinued and the patient is subjected to some stress, he will respond poorly because his pituitary is still inhibited from secreting ACTH. Adrenal insufficiency may thus come about. The same holds true in the case of prolonged high dosage therapy with cortisone. If the cortisone is discontinued suddenly instead of being tapered off gradually, the adrenal cortex will find itself unequal to meet any emergencies. This occurs because cortisone administered for long periods may produce not only a certain amount of adrenocortical involution, but also an inhibitory effect on the pituitary, an effect which may last for several days after therapy is terminated. In some cases, even exogenous ACTH may fail to stimulate the adrenal cortex if the ACTH is given within one week or 10 days after a long course of cortisone. Hence it is desirable to give the patient a rest of four to six weeks between courses of treatment if possible.

ACTH is available in several forms. As a saline suspension it may be given in doses of 100 mg. per day intramuscularly in five divided doses. As the condition improves, the dose should be reduced to 20 to 60 mg. per day in divided doses. If an immediate effect is desired, ACTH may be given intravenously in doses of 20 to 40 mg. per day in 5 per cent glucose in distilled water by continuous drip at the rate of 30 drops per minute or about 3 liters per day. This method is obviously inconvenient and has definite limitations although it is very effective in some allergic diseases, especially in status asthmaticus. We have used it on only a few occasions. ACTHAR® gel is available in 1 cc. doses containing 20 I.U. (international units) and 40 I.U. per cubic centimeter. The initial dose is 20 to 40 I.U. daily or twice a day injected intramuscularly. The dose may be reduced to 10 I.U. every other day as clinical improvement is obtained. This method of treatment is desirable in instances of severe contact dermatitis or in instances where it is not possible for the patient to take more frequent injections or where for other reasons it is not desirable to give cortisone by mouth.

Cortisone (cortin) is available as a saline suspension for intramuscular administration in 1 cc. vials containing 25 mg. per cubic centimeter and in 20 cc. vials. For oral use the tablets contain 25 mg. each or 5 mg. each. If a rapid effect is desired, the initial daily dose is 300 mg. intramuscularly given in three divided doses at eight hour intervals. This dose is cut on subsequent days to 200 mg. and then to 100 mg. per day in divided doses as the patient improves. If no urgency exists, one may prescribe 100 mg. daily in divided doses. Occasionally, oral administration may be more effective than the intramus-

cular. A maintenance dose of 100 mg. per day is sufficient. Cortisone is also available for ophthalmic allergic conditions as a 0.5 to 2.5 per cent saline suspension and also as an ophthalmic ointment. Some local allergic conditions of the eye respond well to such local application.

In another form it is available as compound F (hydrocortisone or hydrocortone) in 5 cc. vials containing 25 mg. per cubic centimeter. Recent literature indicates it is more slowly absorbed and more effective when injected locally as in involved joints. It is perhaps somewhat more potent than cortisone. We are now studying its effect in experimental allergic conditions. Parenterally administered cortisone is absorbed slowly. Hence, it becomes necessary to continue with small doses of oral tablets for the first 24 hours when changing from oral to parenteral method of administration. Similarly, when changing from the parenteral to the oral method it should be remembered that for the first 24 hours after the change is made there is still some absorption of the hormone and therefore the oral dose need not be very high.

We have not always found it necessary to use the same dosage for infants and children as for adults. In general, we have found two-thirds of this dosage sufficient for our needs in the maintenance treatment of most allergic conditions in children. ACTH may be used intravenously on the rare occasions when it seems necessary for infants and children, in doses of 10 to 60 mg. per day.

The question naturally arises, when should one prescribe ACTH and when should cortisone be given? What are the relative indications for each? The clinical and metabolic effects of ACTH are analogous to those obtained from cortisone if a normally responsive adrenal cortex is present. In acute emergencies and during periods of immediate stress, as in the case of status asthmaticus, the adrenal cortex is overly active. The circulating eosinophils may drop as a result of this, and this drop itself is an indication of adrenocortical response to stress and strain. In such situations, it stands to reason that there is no point in further taxing and exhausting the adrenal cortex by overstimulation with ACTH. Cortisone is the drug of choice. However, we give ACTH in more chronic conditions where a more immediate effect is desired. Also, ACTH is administered intravenously if there is an indication for a quicker therapeutic effect. If the adrenal cortex is not responsive, there is no point in prescribing ACTH—for under these circumstances it will not bring about increased adrenal corticoid secretion.

Clinical Value of ACTH and Cortisone

In a general way, ACTH and cortisone exert a profound effect on the reversible phases of most of the allergic states. The local edema, the early morphologic changes of eczema (vesicles, maculas, etc.) and the severe pruritus which accompany the various allergic dermatoses invariably diminish or disappear. The edema of the nasal mucous membrane and of the bronchi and bronchioles is lessened in nasal allergy and asthma with resulting functional improvement. The early inflammatory changes of lupus erythematosus and periarteritis nodosa subside. Furthermore, as a result of pretreatment with ACTH and cortisone constitutional reactions (asthma) which may be brought about from overdosage with the respective antigen are lessened or eliminated. The local tuberculin reaction may be inhibited if the test is performed following pretreatment with these hormones. The local skin histamine reaction is not affected, and the positive direct skin test is only slightly affected.

There have been many reports on the effect of ACTH and cortisone in the treatment of various allergic conditions.[17-23] Following is an account of our own experiences in this connection. We shall not go into details, nor will we give separate case reports to illustrate our conclusions.

Hay fever and allergic rhinitis—ACTH and cortisone are not indicated in the treatment of these conditions. They should be prescribed only in the severe acute emergencies encountered occasionally in nasal allergy. Nasal polyps disappear entirely. Nose drops of cortisone 0.5 per cent are not effective.

The effect of hormone therapy is only transient in hay fever and allergic rhinitis. Hyposensitization and avoidance therapy are still the procedures of choice.

Bronchial asthma[24]—Adrenocortical steroid therapy is indicated in severe intractable asthma and status asthmaticus. ACTH intravenously is to be given only in very severe instances where immediate effect is desired. Cortisone tablets may be used for maintenance. All other therapy should be stopped at this time. The hormones are not effective when thick, inspissated, mucopurulent secretion produces mechanical obstruction of the bronchi. Bronchoscopy should be done in these cases. Nor is hormone therapy justified as routine asthma treatment. We could find no advantage to aerosol cortisone therapy (25 mg. per cubic centimeter). Relapses often occur when treatment is stopped. Pulmonary function tests indicate improvement which parallels the clinical results.

Serum disease pattern reaction—Allergy to serums and drugs is quickly controlled with cortisone and ACTH. Such treatment is usually not necessary because the condition is easily managed with other procedures. The hormones are indicated in the more acute and severe reaction, i.e., accelerated serum disease type of reaction or sudden atopy to drugs and serums. Their use may be lifesaving in cases of this type.

Atopic dermatitis—Infants and children show marked transient improvement especially after all other forms of therapy have failed to give the patient any relief from the severe pruritus. Treatment is of value only if the secondary skin changes are not too marked.[21] Two per cent ointment of cortisone is ineffective locally. Again, the hormones are to be used conservatively and sparingly in these cases only in the very acute phases of the disease and not for long periods.

Urticaria and angioedema—In many instances where other symptomatic therapy fails, the results from hormones are dramatic. This is particularly true in threatened edema of the glottis where the patient's life may be saved by this treatment. In such instances, the patient may take cortisone by mouth.

Collagen disease—Periarteritis nodosa, lupus erythematosus disseminatus, rheumatic fever and rheumatoid arthritis[29,47] are the collagen diseases in which adrenal corticosteroids are effective. Little need be said here about their value in rheumatic fever and rheumatoid arthritis for there is a great deal of information on the subject. We have found that ACTH and cortisone are of great value in the other two collagenous diseases mentioned because they help to tide the patient over the acute fulminating phase of the disease, thus perhaps bringing about a remission. They do not effect a cure. The early, reversible, inflammatory changes found in periarteritis nodosa and in lupus erythematosus may disappear. The late, established changes, however, remain unaffected.

Contact dermatitis (allergic)—This condition is usually controlled by other therapeutic agents. If very severe and widespread, ACTH or cortisone may be given. We have found acthar gel very effective in these cases. As a rule, the vesicles disappear and the pruritus stops soon after therapy is instituted.

ACTH and cortisone are contraindicated in the presence of peptic ulcer, tuberculosis, psychotic conditions, acne, furunculosis and Cushing's syndrome.

Discussion—The mechanism of the beneficial action of these hormones in allergic diseases is not altogether understood. We have shown[48] that under certain conditions cortisone depresses the precipitin titer found during sensitization. This has also been shown by others.[49] This reduction in antibody titer may be due in part to the fact that the hormones produce a negative nitrogen balance by decreasing the synthesis of proteins from amino acids.[50] Or, it may be connected with the depression of lymphocytes[51,52] and of fibroblastic proliferation,[53] for both the lymphocytes and the fibroblasts are part of the reticuloendothelial system. ACTH has, however, no effect on the rate of disappearance of passively transferred antibodies.[54] It is interesting to point out that in spite of the slight reduction in the precipitin titer observed by us in cortisone-treated animals, as mentioned previously, the incidence and severity of the

Arthus phenomenon and of anaphylactic shock remained unaffected by cortisone. Germuth and Ottinger[49] and Fischel[55] have obtained contradictory results in this connection. There is no definite evidence that cortisone affects the immunologic reaction in man. It does not reduce antibody formation or enhance antibody destruction. The level of skin-sensitizing antibody is not decreased. In our hands, the immediate skin reaction to specific antigens is not reduced although Bowman, et al.[56] show that there is a very slight depression in this reaction. While patients sensitive to certain substances are shown to tolerate increased amounts of these antigens when under treatment with ACTH or cortisone, they do not show an altered skin reaction to the nitrogen or to histamine, demonstrating the fact that the reduction in clinical sensitivity is not necessarily a reduction in sensitivity to histamine—the liberation product of antigen-antibody union—nor is there any evidence than antigen-antibody union is prevented.

Some of the collagenous diseases—acute lupus erythematosus disseminatus, periarteritis nodosa and serum disease—react promptly to hormone therapy. Similarly, there is a suggestion that other diseases of hypersensitivity which may be related to the above conditions, namely, acquired hemolytic anemia and thrombocytopenic purpura, may also be affected somewhat by cortisone.[18-20]

It is likely that the mechanism by which ACTH and cortisone mediate protection in these conditions is similar. In all probability it is, in light of the present available evidence, not a specific immunologic mechanism.

Cortisone may reduce tissue histamine and in some way, probably through its effect on hyaluronidase, affect the spreading factor. It appears that the hormones act at the cell level. Just what they do is not clear. At any rate, the cell is protected against the injurious effect of antigen-antibody union just as it may be protected against other noxious agents. Thus, the established organic changes of disease are not affected. However, the reversible phases of the allergic condition are controlled and the manifestations of cell injury are reduced. It remains for the future to enlighten us more specifically in this regard.

In all these acute exacerbations of chronic allergic disorders, ACTH and cortisone help the patient over the acute, refractory, intractable phase of the disease, giving him new hope and confidence in his future outlook and thus encouraging him to undertake further study of etiologic factors. *Hormone therapy is not a substitute for adequate allergic diagnosis and treatment.*

Summary and Conclusions

A brief review has been presented of the present available information on ACTH and cortisone with respect to (1) physiology of adrenal cortex; (2) physiologic and metabolic effects of adrenocortical steroids; (3) precautions and procedures to be employed prior to and during ACTH and cortisone therapy; (4) dosage and methods of administration. and (5) therapeutic results from the use of ACTH and cortisone in allergic disease.

ADDENDUM: Since the above article was written it has become apparent that asthmatic patients can tolerate relatively large doses of cortisone. Some reports have appeared which indicate that small doses of cortisone given together with antihistaminics are beneficial in the treatment of hay fever. Cortogen acetate (Schering) is now available in doses of 100 mg. daily by mouth or by intramuscular injection. This preparation is marketed in the form of tablets of 25 mg. each, or for intramuscular administration in vials containing 25 mg. per cubic centimeter.

The references cited in this article will appear in the author's reprints.

The Role of Surgery in Peptic Ulcer

ALEC HORWITZ*

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Peptic ulcer is a psychosomatic disease, and there must be a distinct and definite indication for surgical treatment. Many patients need reorganization of their lives rather than of their stomachs. If a patient cannot talk himself out of it with the help of a psychiatrist, or eat his way out of it by diet, then the surgeon is called in. Whether the operative procedure should be a subdiaphragmatic vagotomy with a supplemental drainage operation, or an 80 per cent gastric resection, is still controversial, with the tendency away from vagotomy and toward resection.

ALEC HORWITZ

It is generally accepted that 85 per cent of patients with peptic ulcer can be treated satisfactorily by medical means.[1] Surgical intervention is reserved, therefore, for the other 15 per cent who for one reason or another are no longer amenable to medical care. This small group will consist of (1) those with complications such as perforation, obstruction and hemorrhage, (2) a small number who will not or cannot be rehabilitated by adequate medical therapy and (3) those whose ulcers are located on the gastric side of the pylorus.

Gastric Ulcer

Gastric ulcers differ from duodenal ulcers in many other respects besides location. The hypersecretion of acid gastric juice is four times greater in gastric ulcer than in duodenal ulcer. The average size of the gastric ulcer is five times that of duodenal ulcer. Both occur at any age, but the highest average incidence is in the fifth decade of life for gastric ulcer and in the fourth decade for duodenal ulcer. Although some would consider the two as separate disease entities, Hollander[2] has stated that the clinical differences can be explained by the difference in location, which evokes a different physiologic response.

All this would be only of passing interest were it not for one very important difference—the danger of malignancy. That danger lies not only in the fact that about 2 to 5 per cent of gastric ulcers may become malignant, but also in that the benign ulcer and the ulcerating carcinoma are very often indistinguishable. The problem has been very well stated by Balfour:[3] "The question of the percentage of gastric ulcers becoming malignant is purely academic, and the most important and practical issue underlying the whole problem is that there are no known criteria by which the clinician, the roentgenologist, or the surgeon can decide definitely the exact nature of a given ulcer. Microscopic examination alone will reveal its nature."

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Again Balfour[3] states: "Our experience repeatedly has taught us the necessity of considering carcinoma when a gastric lesion is present." The reasons for this are summarized as follows: (1) Gastric carcinoma is the most frequent cancer in man, and is four times more frequent than gastric ulcer; (2) 40 to 50 per cent of surgically and histologically verified gastric cancers have an antecedent typical or strongly suggestive ulcer history; (3) in 30 per cent of all cases of carcinomatous ulcers the roentgenologist is unable to state the exact nature of the lesion, and (4) even carcinomatous ulcers will heal temporarily or improve greatly with good medical treatment.

There are other good reasons for considering surgery the treatment of choice in gastric ulcer. Only one out of every four or five gastric cancers is resectable, and of every 100 patients with gastric cancer that come to the physician only 1 will be alive five years later. However, if we consider only those who have carcinomatous ulcers and undergo resection, 15 per cent—and some say even up to 40 per cent—will be alive five years later. If we are to improve the extremely low cure rate in gastric carcinoma it is imperative that we see these patients early.

A six week trial of medical treatment, as advocated by some, may spell disaster. Temporary improvement, both clinically and roentgenologically, may lull one into false security. Another six weeks may pass or the patient may not be seen for a long period of time, and the next examination may reveal an inoperable lesion. If Smith and Jordan's[4] large series of gastric ulcer cases is studied, it will be noted that more than half the patients have recurrence of symptoms, or bleed, obstruct or perforate—complications which, all admit, are indications for surgery.

The question now arises, what can we offer the patient as to surgical mortality and morbidity? The two greatest factors influencing mortality and morbidity in gastric resection for peptic ulcer are (1) the difficulties in closing the duodenal end and (2) the possibility of postoperative marginal ulcer. These two factors are almost absent in gastric resection for gastric ulcer. Gastric resection for gastric ulcer results in 100 per cent achlorhydria, and gastrojejunal ulcer is practically unknown. The duodenal end, not being involved in any ulceration or induration, is easily dealt with. The mortality rate in a review of large numbers of cases is only from 1 to 2 per cent.[5]

We must conclude, therefore, that every gastric ulcer is a surgical problem unless there are definite contraindications to surgery. In the extremes of age and in those few cases in which the benign nature of the lesion is incontrovertible, medical treatment may be tried for several weeks.

Gastric resection with removal of the lesion is the desired surgical treatment. However, in those cases where the lesion is very high up on the lesser curvature near the cardia, the treatment must be individualized. The risk of removing a very high lesion or the necessity of performing a total gastrectomy must be weighed against the risk of leaving a possible cancer. Colp and Druckerman[6] and Finsterer would do a biopsy and then a subtotal gastric resection. They claim that the unremoved ulcer will heal if benign. Others[7] would do a biopsy and then a vagotomy and gastroenterostomy. Since hypersecretion is not a problem in gastric ulcer, we cannot subscribe to such treatment.

Perforation

In 1930 Singer and Vaughan[8] coined the term "formes frustes" type of perforation to describe cases in which perforation occurs and, after several hours, becomes sealed over. Occasionally, in patients with mild abdominal symptoms, air would be seen under the diaphragm on roentgenologic examination, and on later examination a peptic ulcer would be found. The treatment in those cases was nonsurgical unless there was a question of nonhealing.

In 1935 Wangensteen[9] advocated nonoperative treatment and the use of nasogastric suction in doubtful cases, in those in which the perforation had become localized and sealed off, in the very late cases and in very bad risk patients. The nonoperative treatment has

since been resurrected by Bedford-Turner, Visick, Bingham and Seeley. A review[10] of the work of Turner, Taylor, Baritell, Brick and Bingham showed 78 cases with 5 deaths. Some of these, however, were selected cases. Bertram reported 16 consecutive cases of perforated duodenal ulcer with no deaths.

Seeley,[11] reporting on 106 cases—105 of which were duodenal ulcers and 1 a perforation of the stomach with the gastroscope—had a corrected mortality of 0.9 per cent. Other workers, whose studies are quoted by Seeley, had less fortunate results. Truscott and Withycombe reported a mortality rate of 15 per cent, and Bingham 11.3 per cent. Seeley does not advocate nonoperative treatment as a supplantation for surgical intervention, but rather as a comparative study before a conclusion is reached.

Beattie[12] reported 40 cases, of which 31 of 32 duodenal ulcer patients recovered, 4 out of 5 gastric ulcer patients died, and 1 had a perforating carcinoma. He has since given up the nonoperative treatment.

Collins[13] quoted comparative figures he had compiled, as follows: for nonoperative treatment, 11 authors, 191 cases, 25 deaths—a mortality rate of 11.6 per cent; for operative treatment, 10 authors, 1,201 cases, 49 deaths—a mortality rate of 4.1 per cent. "These figures leave little doubt in the unbiased mind that immediate surgical closure of a perforated gastroduodenal ulcer is still the best and safest method of treating these acute lesions."

There are some who would do a definitive gastric resection in the presence of an acute perforation.[14-18] Although this method may be feasible in the very occasional case, most surgeons would condemn it as too radical.

Auchincloss[19] reported 13 cases in which immediate subtotal gastrectomy was performed for acute perforated peptic ulcer, with no deaths. Nearly all the patients were operated on less than 12 hours after perforation, and cultures showed no growth in any case. He advised that subtotal gastrectomy be considered in all cases unless a definite contraindication exists. He further advised that gastrectomy be done if at all possible if a gastric ulcer is found, if hemorrhage is a concomitant factor and if simple closure will threaten a complete obstruction of the pyloric canal or duodenum.

Dodson[20] would make use of the fact that operation done 7 to 14 days after an initial trauma alters the metabolic response and accelerates wound healing. He advises simple closure and then definitive subtotal gastrectomy 7 to 26 days later. He reported 8 cases with good results. The wounds healed rapidly, and subjectively the patients felt better and had a smoother convalescence.

The accepted treatment is immediate operation and simple closure. The mortality rate in selected cases is from 1 to 5 per cent but the over-all mortality is still too high. No doubt there will be some patients who should be treated by nasogastric suction, antibiotics and the usual Ochsner treatment for peritonitis. This treatment, as Seeley has pointed out, is very meticulous and must be carried out with extreme care and constant attention to detail. Seeley's reports are from a large Army medical center where such ideal care may be obtainable, but this is not always the case in civilian hospitals. The advantage of nonoperative treatment is that it avoids unnecessary operations in the presence of those conditions that mimic a perforation, such as acute pancreatitis or coronary thrombosis. The disadvantage, however, is that some other surgical conditions may be missed which urgently need intervention. Again, whereas the nonoperative treatment may be adequate in patients with duodenal ulcer, it has been quite unsafe in cases of gastric ulcer and could be disastrous in the presence of perforating carcinoma.

More important is the follow-up treatment. Turner[14] has emphasized in his study of 141 patients that 85 per cent have symptoms postoperatively—bleeding or obstruction in one-third, and reperforation in 6 per cent. Elective, 75 to 80 per cent gastric resection three to six weeks postoperatively is the advisable treatment.

Obstruction

The fact that an ulcer patient vomits does

not mean he has an obstruction. Vomiting may be of the reflex variety. Roentgenologic examination shows no retention of gastric contents in these cases. Then there is the vomiting due to pylorospasm or antral spasm. These have been spoken of as due to "edema." Rather than edema, these patients suffer from hyperirritability of the antral and pyloric portions of the stomach. Roentgenograms show some retention, but after a lapse of some time there is complete emptying. Both these types are amenable to temporary medical treatment; most of them eventually come to surgery.

When vomiting is persistent even after treatment, and roentgenologic examination shows 6 or even 12 or 24 hour retention, the obstruction is due to cicatrization, and actual obstruction, either in the duodenum or pylorus, or even hourglass deformity of the stomach, will be present.

The treatment of such obstruction is surgical, but surgery without proper preparation will result in a very high mortality rate. The stomach is filled with foul gastric residue, the walls are edematous and do not lend themselves to suturing, and leakage and peritonitis follow any attempt at surgery. Many of these patients are extremely ill. They are dehydrated, have low blood volume and approach the shocklike state. The urine is scanty, the patients are drowsy and listless, the skin is dry and the abdomen is scaphoid. Many go on to uremia or show evidence of gastric tetany. In such a case, a tube inserted into the dilated stomach which may reach the pelvis will produce several thousand cubic centimeters of foul-smelling gastric contents.

The blood chemistry is also revealing. There is marked azotemia, low plasma chlorides and high carbon dioxide-combining power, approaching the values for alkalosis. If it is over 100 per cent by volume, tetany is often imminent. Study of the serum proteins will show low levels for the albumin and globulin, and at times there is a reversal of the ratio.

The preoperative treatment of such patients is most important. The stomach must be emptied and kept empty. This is best accomplished by the indwelling Levin tube. The stomach is washed out with saline solution and the patient is allowed sips of water to keep the throat moist and the tube clear. No more than 1000 cc. is allowed orally so as not to remove too much of the stomach acid and precipitate an alkalosis. Maintenance of electrolytic balance is sought by proper administration of replacement fluids, proteins, serum albumin and blood. An attempt is made to obtain a flow of 1000 to 1500 cc. of urine daily. Vitamins are added to the parenteral fluids, especially B complex and C.

After a 24 or 48 hour interval of such treatment, a retention diet is begun. This diet consists of liquids of high protein and caloric value, such as strained cream soups, cocoa made with half-and-half milk and cream, plain gelatin, POSTUM®, etc., all of which can be aspirated through a Levin tube. These are fed in 200 cc. amounts every two hours from 6 A.M. to 8 P.M. The stomach is aspirated just before the first feeding and before every fourth feeding. The last aspiration is made just before midnight to obtain an empty stomach for the night. The amount aspirated is subtracted from the amount given orally. This gives the clue as to the severity of the obstruction. It is surprising how often a good deal will pass through, and sometimes the obstruction may relent sufficiently to solve the problem of protein stabilization.

If the plasma chlorides are persistently low and the carbon dioxide-combining power is high, there may be low potassium values. Cautious administration of potassium, after the heart has been checked by electrocardiography, may ameliorate the condition.

With the patient in the best possible electrolytic balance, and his protein level raised, the operation of choice is gastric resection. If the patient is elderly and is a poor risk, no apology need be made for doing a gastroenterostomy, under local anesthesia if necessary. In extremely ill patients a jejunostomy may be necessary as a preliminary to more definitive surgery.

Hemorrhage

Bleeding from a peptic ulcer may be mild

or severe. In the mild type the bleeding may be occult, and this is reflected in anemia, weakness and lassitude. Occasionally there are small repeated hemorrhages, with tarry stools or mild hematemesis. These cause a mild immediate reaction, more psychic than physiologic, and a mild anemia is noted a few days later. If this warning goes unheeded, and emotional, physical or other undue strains coupled with dietary indiscretions or alcoholic excesses are superimposed, then a massive hemorrhage may occur.

Massive bleeding is dramatic and dangerous. It may be ushered in with marked pallor, cold sweat and repeated syncopal attacks. These may be preceded or followed by one or more large tarry, black stools, followed by stools containing reddish blood. Sometimes tarry stools go unnoticed or unheeded for several days and the dramatic moment is ushered in with marked hematemesis. The amount of blood loss varies. It has been proved that it takes at least 60 cc. of ingested blood to produce a tarry stool, and at least 350 cc. to produce symptoms.[21]

Statistics vary widely as to the frequency of gross bleeding from peptic ulcer. Of 2400 patients admitted to the Johns Hopkins Hospital with peptic ulcer, 9 per cent presented this finding. Heuer reported that 21 per cent of ulcer patients admitted to the New York Hospital were admitted chiefly because of bleeding. At the Mayo Clinic 17 per cent of operated duodenal ulcer patients and 25 per cent of operated gastric ulcer patients gave a history of bleeding. Eliason and Ebling reported an incidence of 19.5 per cent of 546 cases of duodenal ulcer and 39.1 per cent of 92 cases of gastric ulcer.[22]

Hemorrhage occurs predominantly in males, the ratio being 5 to 1. In my own experience, massive hemorrhage from peptic ulcer occurs in the plethoric, obese male with a wide costal margin, a patient such as one would surmise would be a candidate for gallbladder disease.

About three-fourths of the patients with bleeding ulcer give a history consistent with peptic ulcer. The presence of concomitant pain is thought by some to be of grave import. Others report that pain and other symptoms disappear quite often after recovery from hemorrhage. According to Mage,[23] painless bleeding from a marginal ulcer signifies a superficial ulcer, and the presence of pain indicates penetration and possible impending perforation. Perforation may occur simultaneously in 10 per cent of the bleeding ulcers and is of very serious prognostic importance.[22]

The source of bleeding in a massive gastrointestinal hemorrhage is very important. In 90 per cent of all cases of gastric hemorrhage the bleeding is due to intrinsic gastroduodenal lesions; 70 to 80 per cent are due to peptic ulcer, and 50 per cent are due to duodenal ulcer. The other more frequent causes of bleeding are esophageal varices of portal hypertension, and the blood dyscrasias.

The treatment of massive hemorrhage is very controversial. Statistics are cited to support each contention, but since the definitions of massive hemorrhage are not identical, the statistics are not comparable. Some believe that bleeding sufficient to cause syncope and not the red cell count is the deciding factor.[24] Others base their statistics on a red cell count of 3,000,000 or less, a systolic blood pressure of 90 or less and a pulse rate of 130 or more.[25] Still others insist that the red cell count be 2,500,000 or less. This small change accounts for a change in mortality of 5 per cent. Again the elapsed time between the bleeding episode and the determination of the red cell count is so important, yet so inaccurate, that the reliability of such an index is questionable.

In the past, massive hemorrhage was generally treated by starvation, ice bag to epigastrium, and heavy sedation with morphine. Transfusions were given rarely and sparingly, not more than 250 cc. at one time, so as not to raise the blood pressure and disturb the clot. In 1918 Finsterer[26] of Vienna urged early operation in all cases of acute, profuse bleeding in chronic ulcer—in the first 24 to 48 hours. Gordon-Taylor[27] termed this the "golden period." Finsterer claimed this method would avoid lethal bleeding and fatalities from perforation. After the lapse of 48 hours

the mortality rate rose steeply because of parenchymatous degeneration of vital organs, especially the liver, from anoxemia. He reported on 86 private patients who underwent gastric resection, with only 2 deaths or 2.3 per cent mortality, and on 95 ward patients, with 4 deaths or 4.2 per cent mortality. After 48 hours the surgical mortality rate rose to more than 20 per cent.

Meulengracht,[28] on the other hand, reported his experience with about 1000 patients with bleeding ulcer treated by his special diet and medical regimen, with only a 2.5 per cent mortality. But the statistics here are dubious because many of these cases would not fall in the usual category of massive hemorrhage.

Following these various reports, it became clear that not all patients with bleeding ulcer should receive the same treatment, and that a definite number of patients would continue to bleed regardless of adequate medical treatment. If the internist insisted on keeping the patient until he was moribund and then rushed him to the surgeon, the mortality rate became appalling—from 50 to 75 per cent. What should have been reported as salvage was called surgical mortality, and put surgical treatment into disrepute. The problem was to discover which patients would and which would not stop bleeding under medical treatment, so as to be able to institute surgical treatment earlier for those who needed it. A closer study of those patients who continued to bleed despite treatment disclosed certain factors which could be used in recognizing them earlier.

It was noted that patients over 45 or 50 years of age were prone to continue bleeding; that the mortality rate for those over 50 rose sharply; that gastric ulcers bled more profusely, and that the mortality rate increased greatly if surgery was instituted after the first 48 hours. The complication of obstruction in a bleeding ulcer was an indication for surgery, and that of perforation of the gravest importance prognostically.

Various surgeons then began to formulate criteria for surgical intervention. Amendola[25] listed the following: (1) acute bleeding after adequate blood replacement for 24 hours, as shown by dropping hematocrit and blood pressure and rising pulse, in patients over 50 years of age; (2) continued bleeding after 48 hours, in patients under 50 years of age; (3) recurrence of bleeding after the bleeding has stopped, while still under treatment; (4) hemorrhage complicated by obstruction, and (5) hemorrhage complicated by impending or actual perforation.

Amendola's statistics showed 11 patients operated on in the first 48 hours, with 1 death or 9 per cent mortality, and 84 patients treated expectantly, with 13 deaths or 15 per cent mortality.

Welch[30] stated the belief that surgery is indicated at once if bleeding continues after the administration of 2500 cc. of blood. A small group of patients over 50 years of age will usually be in that category. In those stabilized with transfusions, at least 25 per cent will bleed again in three days and should be operated on immediately. His statistics showed 32 cases with 3 deaths among those patients operated on within 48 hours, or about 10 per cent mortality, but 13 cases with 7 deaths or 54 per cent mortality in the late cases. There was only 1 death in 68 cases in which operation was done electively after recovery from hemorrhage.

Bowers and Rossett[31] stated that if surgery is done it must be done within the first 48 hours. According to these authors, surgery is indicated (1) in those patients over 45 years of age with continued bleeding despite feeding and adequate blood replacement, (2) in diabetics, (3) in those with obstruction, (4) in patients with gastric ulcers, (5) in the apprehensive patient and (6) in those with a history of recovery from a previous bleeding episode.

Lipp, et al.[24] insisted that their "test of transfusion" be applied. Their method of treatment consists in giving 2000 cc. of blood in one hour; if there is no response in three hours, surgery is urged immediately. If there is cessation of bleeding they do not hesitate to replace blood, even as much as 5000 cc. in six hours. Their statistics showed 61 cases with 5 deaths.

With the advent of the blood bank, im-

proved anesthesia, better surgical technics and greater understanding of fluid balance and replacement, and finally the antibiotics, surgeons have become bolder in their approach to the problem. Stewart, et al.[32] advocated immediate surgery if there is a diagnosis or a presumptive diagnosis of peptic ulcer as the cause of bleeding. They defined massive hemorrhage as the presence of less than 60 per cent of the total circulating red cell mass. However, they insisted that 3000 cc. of blood be available before surgery is undertaken. These authors reported 65 cases with 7 deaths or 10.7 per cent mortality; of 42 patients who refused operation and were treated expectantly, there were 9 deaths (21.4 per cent mortality). In the last 50 cases only 3 deaths occurred (6 per cent). The average length of time between onset of hemorrhage and surgery was 12 hours. These workers admitted that 1 patient had esophageal varices and bled after surgery and in 2 cases no adequate cause of the bleeding could be shown at surgery. On the other hand, 1 patient had a carcinoma of the stomach and 1 a lymphosarcoma.

It is now well recognized that no fixed rule can be applied to the problem of massive hemorrhage. It is a joint responsibility of the internist and surgeon. Each case should be individualized and a flexible plan can be formulated which will lead to the most favorable outcome for the patient, the surgeon and the hospital.

Confronted with a case of massive hemorrhage, immediate steps are taken to combat shock. Blood must be replaced rapidly, in several veins simultaneously or intra-arterially if necessary, to keep the blood pressure from falling below 100 systolic. Sedation with barbiturates or DEMEROL® and quiet reassurance of the apprehensive patient are important. Pulse and blood pressure readings are recorded every half hour. Blood is drawn for hematocrit and complete blood studies to rule out dyscrasias in the doubtful cases. Some prefer blood volume studies because it takes at least 24 hours for complete hemodilution to occur, and hematocrit studies are therefore less reliable.

As soon as shock is overcome, a painstaking history is obtained with special inquiries about previous hemorrhages. A rapid physical examination is made to evaluate the general physical condition of the patient. In doubtful cases, evidences of dyscrasias, cirrhosis of the liver or malignant disease are sought. A BROMSULPHALEIN® test[29] should be done and is quite valuable in the doubtful case in ruling out cirrhosis. If available, roentgenologic examination by the Hampton[30] technic is very useful. It must be remembered that a cirrhotic individual may still have a bleeding ulcer, as Finsterer[26] has reported.

If no varices are present or suspected, a Levin tube may be used for aspiration. This gives a clue to further bleeding and removes the gastric acid. Some authors prefer to begin feeding a modified Sippy or other similar diet and antacids despite any vomiting.

Blood chemistry studies should be done for comparative purposes and to watch the progress of the patient as well as to allow the intelligent care of fluid balance. Some believe the blood urea level to be of great value in determining the continuation of bleeding. If it continues to be elevated or rises after the first 24 or 48 hours, and there is no kidney damage to explain it, it signifies continued bleeding.

With the regimen of immediate and adequate blood replacement before hemodilution takes place, and other measures to combat shock and counteract hyperacidity, bleeding will cease in the majority of cases. However, a small number of patients, usually over 50 years of age, may continue to lose blood as rapidly as it is replenished. Surgery should not be delayed more than 24 hours in these cases. If the patient is under 50 years of age, another 24 hours may be allowed to overcome the bleeding before surgery is done. Recurrence of bleeding after it has ceased and while the patient is under active treatment calls for immediate surgery. The complications of obstruction and perforation demand immediate surgical intervention.

Having decided to operate during the bleeding episode, the unanimous surgical opinion is that, if at all possible, an 80 per cent gastric

resection with removal of the ulcer should be done. In very urgent cases it may be necessary to tackle the bleeding area first, and then continue with gastric resection. Temporizing operations have proved unsuccessful. Finsterer[33] has suggested that in the very urgent and desperate cases pyloric occlusion with tamponade for 24 hours, plus a gastroenterostomy, may prove lifesaving.

When the cause of the bleeding is not clear on external examination with the abdomen open, the stomach and duodenum should be opened widely and the bleeding point sought. This is not always successful, and the surgeon then is faced with a very difficult decision. Superficial erosions, gastritis and retracted vessels with a pinpoint opening, which the pathologist may uncover only after perfusion, may be the cause. Some prefer to close the stomach if no bleeding point is found. Others do a gastrectomy if no extragastrointestinal cause of bleeding is found.

The removal of the bleeding duodenal ulcer is imperative if at all possible. This may lead to a very difficult closure of the duodenum. Welch[30] and also Priestley and Butler[35] have made a valuable contribution to the management of this problem. No attempt is made to close the duodenal stump, but a catheter is purse-stringed into the opening and brought out through a stab wound. When the drainage lessens at the end of about 10 days or two weeks it may be removed. We used this method in 2 cases recently with excellent results. If the closure is felt to be insecure, a catheter may be placed for drainage.

Finsterer[26] believes that if a general anesthetic is used, due to the atony of the intestinal tract postoperatively, the bowel should be emptied of old blood by a cecostomy. He believes that the blood is toxic and is the cause of some of the poor results.

If the bleeding stops, the subsequent interval treatment is also important. If the ulcer is duodenal, definitive treatment is undertaken after six weeks. In gastric ulcer, because of the danger of malignancy, surgery is undertaken as soon as it is feasible.

The definitive treatment, according to most surgeons, is 80 per cent gastric resection with removal of the ulcer if possible. Others[37-39] have advocated subdiaphragmatic vagotomy with gastroenterostomy or gastric resection. Many have condemned it.[36] Dragstedt[38] quoted the Jordan[40] report of the subcommittee on vagotomy of the American Gastroenterologic Association—there was 4.1 per cent recurrence of bleeding after vagotomy and gastroenterostomy in 226 cases of bleeding ulcer. The elapsed time since operation is much too short, however, to make any definite conclusions.

Case 1—A 59 year old merchant with a fairly typical ulcer history of 15 years' duration and a 10 year history of recurrent bleeding was admitted to the hospital on July 14, 1943, because of a massive gastric hemorrhage and a large black, watery stool which had caused him to faint. After transfusions and other treatment, an exploratory operation was done 10 days later under spinal anesthesia. A gallbladder filled with stones was found and removed. The duodenum showed no definite ulcer, and as it was about to be opened for further exploration the patient's condition became very critical and the operation was completed as quickly as possible. He was discharged two weeks later, feeling much better.

He was next hospitalized five years later, on April 3, 1948, because of hematemesis and black stools, both of one week's duration. His hemoglobin fell to 26 per cent and his red cell count to 1,630,000 despite numerous transfusions. On April 5, 1948, with the patient in extremely precarious condition, exploration was done under local anesthesia and PENTOTHAL SODIUM®. No definite ulcer could be found and the rest of the gastrointestinal tract was found to be normal. The duodenum was opened and a good deal of blood welled up from what appeared to be a shallow ulcer at the junction of the first and second parts of the duodenum. When pressure above the duodenum seemed to stem the flow, a suture was placed there and the bleeding seemed to abate. Two silk sutures were taken through the area of the supposed ulcer and a pyloroplasty was done at the request of the anes-

thesiologist who insisted on a minimal amount of surgery. The patient was discharged on April 17, 1948, with a hemoglobin of 57 per cent (9.5 gm.).

Several months later, in July 1948, he was readmitted because of hematemesis. After several weeks' treatment he was discharged, having refused further surgery. In November 1948 he was readmitted to the hospital and an 85 per cent gastrectomy was done, with removal of a duodenal diverticulum, confirmed by the pathologist. He was last seen December 17, 1951; he had gained 20 pounds and felt fine.

Intractable Ulcer

As already stated, 85 per cent of duodenal ulcer patients may be amenable to medical care. That does not mean that these are all cured. It does mean that because of a change in their philosophy of life, or in environment or even in treatment, there has been a cessation of symptoms, or that such symptoms as did occur were easily overcome so as not to interfere with usual activities.

Aside from the patients who have perforation, obstruction or bleeding, there is a small group of duodenal ulcer patients who do not improve sufficiently to be able to return to their own environment or their usual activities. Some of these may improve greatly at the hospital, but once back in their own home or at work the old stresses and strains recur and their symptoms recur. These have been called the "intractable" ulcer cases. They are usually men over 40 years of age who have night pain which is often referred to the back and is relieved less and less by food and alkalis.

When should surgery be offered these patients? Many times it is the internist who feels that there is a lack of response to all medical means and that surgery offers the best chance of rehabilitation. We have always felt that unless the patient has been under very adequate medical care and not just given a diet and told not to worry, a definite review should be made of what such care has been. It is surprising how many patients continue to smoke and to drink alcohol, yet think that they are under treatment for an ulcer. It often becomes a question whether the ulcer or the patient is intractable. Dr. C. H. Mayo used to say facetiously, "Surgery should only be undertaken after nine separate, complete and permanent medical cures."[41]

Moore, et al.,[42] after examining the records of about 1000 cases of duodenal ulcer at the Massachusetts General Hospital, objected to the term "intractable" and stated that they would prefer to diagnose the potential failures before they became "intractable." Such cases they would designate as *progressive* or *virulent*, and from their study they advanced a set of primary and secondary criteria for such a diagnosis:

1. Primary criteria
   a. One perforation in the past, with present ulcer symptoms
   b. One acute hemorrhage requiring blood transfusion
   c. Progressive pain over a two year period, with the patient working and under a physician's care and following his advice
2. Secondary criteria
   a. A male patient with duodenal ulcer symptoms and under a physician's care
   b. A male patient with onset of symptoms prior to the age of 20 years or subsequent to the age of 65

If two of these criteria, at least one of which must be primary, are present, the diagnosis of progressive virulent ulcer disease may be considered established, and the outlook for nonsurgical management is poor. If three of these criteria are present, surgery should be urged.

Having decided to offer surgery to these patients, what procedure should be followed? Here there are two very divergent groups: (1) those who advocate subdiaphragmatic vagotomy with a supplemental drainage operation such as gastroenterostomy or pyloroplasty and (2) those who advocate subtotal resection of the stomach, from 75 to 80 per cent, with removal of the ulcer if possible.

Dragstedt[38] reported on the follow-up results of vagotomy for duodenal ulcer in 509 cases. His study covered a period of from one

to seven years after operation. There were 6 deaths in the group. Eighty-two per cent of the patients were reported as being well. Jordan's[40] report for the American Gastroenterologic Association gives a glowing account of the results of the procedure, but the follow-up is not very long. Many surgeons who have employed vagotomy have given it up.[43,44] Most surgeons believe that not enough time has elapsed for a final verdict on vagotomy plus a supplemental drainage operation. All agree that vagotomy alone should be discontinued, and most surgeons feel that at the present time the best protection against recurrence and the best chance for cure can be afforded by a 75 to 80 per cent gastric resection with the removal of the ulcer if possible. The mortality rate for this procedure has been lowered to 2 per cent or less and the recurrence rate is less than 5 per cent. The best indication for vagotomy is a gastrojejunal ulcer after gastrectomy and, if that operation fails, some advocate total gastrectomy.

Case 2—A 44 year old sheet metal worker with a four year history of peptic ulcer with occasional mild hematemesis and positive x-ray findings of duodenal ulcer was admitted to the hospital in November 1947 because of severe epigastric pain which radiated to the back. His temperature was 102° F.

A posterior gastroenterostomy and an appendectomy were done. At operation it was noted that perforation had occurred posteriorly into the pancreas, as shown by an orange-sized mass in the pancreas. Gastric resection was too hazardous at this time.

Six weeks later there was clinical and roentgenologic evidence of a marginal ulcer, and in April 1948 a transthoracic vagotomy was done, resulting in immediate and dramatic relief of pain. The patient gained over 20 pounds in the next four months and boasted that he had not felt so well in the past six years. On roentgenologic examination the marginal ulcer appeared to be healed.

About a year later he began complaining again of substernal burning, and in June 1949, roentgenograms disclosed a marginal ulcer. Gastric analysis showed 70 per cent free hydrochloric acid and 90 per cent total. After failure of medical therapy, in June 1949 the gastrojejunostomy was taken down and the ulcerated jejunum resected, and an antecolic Polya with a Hofmeister modification type of gastric resection was done. About 80 per cent of the stomach was removed. The pathologist reported that 14 cm. of the lesser curvature, 28 cm. of the greater curvature and 3 cm. of the duodenum had been removed. Diagnosis: healed duodenal ulcer, jejunal peptic ulcer and chronic gastritis.

The patient was symptom-free until September 1949, when he began to complain of epigastric pain. No evidence of ulcer was found, however, and the resection was deemed adequate and the stoma functioning well. He was hospitalized several times, but roentgenographic examination was still negative. Psychotherapy was tried but was unsuccessful because of lack of cooperation. In February 1950 he was x-rayed elsewhere and a definite stomal ulcer was found, and on February 25, 1950, a revision was made of the gastric resection, the jejunal ulcer being removed, the afferent loop of jejunum shortened and more of the stomach removed so that no lesser curvature remained and only approximately 10 per cent of the stomach remained. The operation was done through a thoracoabdominal incision. To insure success, a subdiaphragmatic vagotomy was done. The patient made an uneventful recovery, but did complain of persistent pain. For the next eight months he was in and out of hospitals with no relief of his pain. NOVOCAIN® blocks provided only temporary relief. Continued examinations by various roentgenologists failed to show any stomal ulcers. Gastroscopic examination was negative.

Because there was still some free hydrochloric acid, another transthoracic vagotomy was performed in October 1951 by a thoracic surgeon who found a neuroma from the previous vagotomy, and a posterior branch which was resected. There was no relief of pain. Free hydrochloric acid still persisted.

In desperation a transorbital lobotomy was done on December 28, 1951. The patient still complained of pain, but the psychiatrist stated

that the complaints were not very convincing.

Another transorbital lobotomy was done, and was followed by rhinorrhea. It is too soon yet to know the final outcome of this last procedure.

Summary

1. Peptic ulcer, if duodenal, is a medical problem and is surgical only if there are complications or if there is admitted lack of response to adequate medical care.

2. Gastric ulcer is usually surgical because of the danger of malignancy, unless there are definite contraindications to surgery. The danger of malignancy lies not alone in the less than 5 per cent that might become malignant but rather in the inability to distinguish between the benign and the malignant gastric ulcer in about 20 per cent. The fallacy of a few weeks' trial of medical management lies in the fact that the malignant ulcer improves and may even heal temporarily.

3. Acute perforation occurs in about 12 to 15 per cent of the cases. Most surgeons agree that the treatment should be immediate laparotomy and simple closure. Occasionally, in the forme fruste type of perforation, in the very late case or in one in which surgery is extremely hazardous, nonsurgical treatment by nasogastric suction may be indicated. More important is the institution of definitive treatment, which should not be delayed more than six weeks because 85 per cent of the patients will continue to have symptoms, including the complications of obstruction, bleeding or even reperforation.

4. Obstruction due to cicatrization should be differentiated from the irritable and spastic antrum or possible edema. Preoperative preparation in these cases, with special attention to the blood chemistry, is most important. Gastric resection of 80 per cent of the stomach is the preferred treatment. In certain cases of low acidity and old age, no apology need be made for the use of gastroenterostomy. In the very ill patient, a jejunostomy done under local anesthesia for feeding purposes may be necessary before definitive treatment is undertaken.

5. Massive hemorrhage from peptic ulcer is a joint responsibility of the internist and the surgeon. Each case must be individualized. The great majority of patients with bleeding ulcers will respond to medical treatment, but some, especially those over 50 years of age, may continue to bleed. Those patients who fail to respond to adequate medical care and blood replacement within 24 hours—or, if they are under 50, within 48 hours—should be operated on. The complication of obstruction or perforation makes surgery imperative. Recurrence of bleeding while under active treatment calls for immediate surgery. The ideal treatment is resection of 80 per cent of the stomach with the removal of the ulcer if possible. Interval treatment, after cessation of bleeding, should be definitive gastric resection after six weeks in duodenal ulcer and as early as feasible in gastric ulcer. The conclusions as to the permanency of the excellent results reported from the use of vagotomy with a supplemental drainage operation must await the passage of time. Some who have tried this procedure have discarded it and even advise against it.

6. The intractable ulcer is one which does not respond to adequate medical care or recurs as soon as the patient returns to his environment. This usually will be the posterior penetrating duodenal ulcer in a patient over 40 years of age. Moore, et al.[42] believe that these ulcers can be diagnosed before they become intractable, and have termed them virulent or progressive. They have formulated certain criteria which, if fulfilled, would make certain of these patients candidates for gastric resection. Some advocate subdiaphragmatic vagotomy with supplemental drainage operation, but the majority advocate resection of 80 per cent of the stomach with removal of the ulcer if possible. Time will settle the question of vagotomy.

The references cited in this article will appear in the author's reprints.

Toxemia of Pregnancy; Outline of Treatment

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Toxemia of pregnancy is briefly discussed from a physiologic standpoint with emphasis on treatment, an outline of which is presented. Vasodepressor drugs of the veratrum group are used as a valuable therapeutic adjunct.

STANLEY T. GARBER

NEXT to hemorrhage, preeclampsia and eclampsia account for more maternal deaths than do any other diseases in this country today. Resulting placental damage, retroplacental hemorrhage, separation and prematurity likewise exact a high infant toll. It is my purpose to outline a clear, concise, effective method of treatment.

Definition—Toxemia of pregnancy may be defined as an acute vascular disease which appears in the latter half of pregnancy. It is characterized by hypertension, albuminuria and edema. Soon after delivery, the signs disappear, although permanent vascular and renal damage may persist.

Incidence—Eight to 10 per cent of all pregnant women exhibit some form of hypertension.

Classification—For simplification, we have advanced the following classification: (1) preeclampsia; (2) eclampsia, and (3) preeclampsia or eclampsia superimposed on chronic essential hypertension. Many authors include in the classification chronic essential hypertension and chronic kidney disease associated with pregnancy. Since their treatment represents a different problem, they will not be considered here.

Preeclampsia and eclampsia are two stages of the same disease, differing only in that convulsions and coma are present in the latter. The presence of symptoms such as severe headache, nausea and vomiting, vertigo, blurring of the vision, epigastric pain and twitching denotes a far advanced or severe preeclampsia which may be bordering on the convulsive stage. Because the mildest case may become severe or reach the convulsive stage at any time, we no longer distinguish between so-called mild and severe cases.

Etiology—The cause of the disease has not been determined.

Pathogenesis—A generalized underlying abnormal vasopressor activity or arteriolar spasm is characteristic of preeclampsia. It occurs within the precapillary arterioles and produces (1) diminished blood flow (anoxia); (2) increased capillary permeability (edema and stasis), and (3) changes in the vessel walls (thrombosis, hemorrhage, ischemic necrosis). The entire process may be retrograde, the amount of necrosis depending on the collateral circulation of the particular organ involved.

When we apply this process to specific organs,

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particularly to the brain, eye, liver, kidney or uterus and underlying placenta, it is not difficult to appreciate the seriousness of the disease or to understand the origin of its varied symptoms and signs.

Treatment

Formerly, preeclamptic and eclamptic patients were treated only when there was evidence of terminal symptoms and signs—multiple convulsions, prolonged unconsciousness and pulmonary edema. By studies directed at the disturbed pathophysiologic phenomena in these individuals, we have progressed in our knowledge of the underlying abnormal vasopressor activity from which result the varied symptoms and signs. The inciting mechanism is still undetermined. A high protein, low sodium diet with liberal fluid intake may reverse the process in some cases.

Together with pathophysiologic studies, the vasodepressor activity of various drugs has been observed and tested. Among these, the veratrum alkaloids, used empirically but effectively for many years in Cincinnati, remain unsurpassed to date in overcoming the abnormal arteriolar spasm in preeclampsia and eclampsia alone or when superimposed on pre-existing chronic hypertension. When given intramuscularly, or preferably intravenously, in 5 per cent glucose in distilled water, veratrum produces a marked arteriolar vasodilation with a consequent drop in blood pressure. It recently has been demonstrated that veratrum preparations do not act on the veins. Hence postural hypotension is not present as with sympathetic blockading agents such as tetraethylammonium chloride and spinal anesthesia. The drug also does not affect the cardiac output. Urinary output is temporarily decreased but is subsequently and soon compensated by a marked polyuria. The temporary decrease is harmless to the patient. Thus the available evidence indicates that an integrated arteriolar vasodilation with a decrease in peripheral resistance and increased blood flow to major organs are the result of veratrum administration. Improvement of the circulation occurs and better oxygenation results. The vicious cycle of abnormal vasoconstriction, diminished blood flow, anoxia, thrombosis, edema, hemorrhage and necrosis is broken. Convulsions cease without sedation—other than magnesium sulfate, which is of benefit.

Fluids, from 3000 to 5000 cc. daily, are given with excellent diuretic effect. This condition is not comparable to lower nephron nephrosis, either pathologically or clinically, and does not require the same treatment.

We feel that sedatives in large amounts, as employed almost universally elsewhere, obscure and prolong unnecessarily the unconscious state, contributing definitely to respiratory embarrassment and pulmonary edema.

Specific Treatment

Specifically, the treatment resolves itself into three main categories: (1) preventive and supportive measures; (2) therapeutic measures, and (3) termination of pregnancy.

Preventive and supportive measures—This phase of treatment consists primarily of three important factors, namely, education, diet and rest. Early prenatal care is imperative. Fluid intake should consist of 3000 to 5000 cc. daily. Weight gain should be limited to 20 pounds. The diet should be high in protein, low in salt (no soda), and should contain adequate vitamins. For severe edema, magnesium sulfate, 1 teaspoon in water every other morning, or ammonium chloride, 8 gm. daily for three to four days, may be given.

Therapeutic measures—The patient should be hospitalized for control. The preventive and supportive measures already described should be applied, plus the following: Magnesium sulfate is given for sedation—5 cc. of a 50 per cent solution given intramuscularly every six hours, 10 cc. for eclamptic patients. At bedtime a barbiturate may be given in small amount.

Vasodepressor substances (veratrum) are given as follows: Dilute 0.2 cc. (3 minims) VERATRONE® or 1.0 cc. VERENTERAL® to 10 cc. with 5 per cent glucose in distilled water and give as a single acute injection over two to three minutes into the intravenous tubing of previously started 1000 cc. intravenous infusion of 5 per cent glucose in distilled water. Record blood pressure and pulse at 5 to 10 minute intervals. If response is minimal, repeat after 30 minutes. Forty-five minutes to an hour after the first acute

injection, add veratrum to the infusion bottle as follows: 0.2 cc. veratrone per 100 cc. of 5 per cent glucose in water, or 1.0 cc. verenteral per 100 cc. of 5 per cent glucose in water. Run in at the rate of 75 to 100 cc. per hour. Record blood pressure and pulse hourly. Increase or decrease rate according to hourly blood pressure and pulse levels. After 8 to 48 hours, when well controlled, discontinue intravenous infusion of veratrum. Start intramuscular injections and continue until two to three days post partum as follows: 0.2 cc. to 0.35 cc. (3 to 5 minims) veratrone, or 0.2 cc. VERAFLEX®, given every two hours for pulse over 70 (blood pressure 140/90).

Note—Nausea and vomiting, burning sensation and diaphoresis may be noted as harmless side effects of the drugs. Bradycardia, if marked, may be easily controlled by the intravenous injection of 1/200 gr. atropine.

Termination of pregnancy—No attempt is made to terminate the pregnancy before 48 hours, often four to eight days. Frequently labor supervenes spontaneously during the stabilization or waiting period. Depending on stage of gestation, response of patient to therapy, quantity of albuminuria, condition of infant and status of the cervix, one may either induce labor (stripping of membranes or rupture) or perform cesarean section.

Summary

The ideal treatment for preeclampsia and eclampsia awaits the discovery of the basic etiologic process. In addition to the preventive, supportive and therapeutic measures outlined, the vasodepressor drugs offer an adjunct to the treatment which has proved to be of decisive value.

Veratrum has been employed in Cincinnati for nearly 50 years. During the last 20 years the treatment outlined has been employed continuously with few minor variations. During this time, 205 consecutive eclamptic patients have been so treated. Three patients died, an uncorrected maternal mortality rate of less than 1.5 per cent. Early in the series, 2 patients, poorly handled, died from sepsis long after the eclampsia was well under control. One maternal death resulted from eclampsia per se, a maternal mortality rate of less than 0.5 per cent.

Postgraduate Clinical NOTES

6. LEG CRAMPS IN PREGNANCY

1. Muscle cramps in the legs occur in half of private obstetric patients, most often between the twenty-fourth and thirty-fourth weeks of pregnancy. In a semi-indigent group, the frequency is much lower, probably because of a reduced intake of phosphorus-containing proteins.

2. Large quantities of milk or dicalcium phosphate cause a predisposition to muscular tetany. The consumption of milk causes a fall in diffusible calcium and a rise in the inorganic phosphorus concentrations of the blood. Shifts of the acid-base balance toward the alkaline side may be contributory.

3. Leg cramps may be either prevented or relieved to a significant degree by (a) reducing the intake of milk, (b) the use of calcium salts free of phosphorus, or (c) adding small quantities of aluminum hydroxide gel to the diet in order to remove some of the dietary phosphorus from the intestinal tract.

4. The reduction of milk and the addition of aluminum hydroxide gel to the diet relieves leg cramps by causing a rise in the ionizable calcium concentration of the blood.

Page and Page: Leg Cramps in Pregnancy, *Obstetrics and Gynecology*, 1:99 (January) 1953.

Misconceptions Leading to Delay in the Diagnosis of Intracranial Space-Taking Lesions

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To "hold the mirror up to nature" is an instructive process. The author, who spent more than three years in one of our smaller cities, far from a medical school, creating a neurosurgical practice where none had previously existed, attempts to describe what he found there.

W. R. CHAMBERS

MORE and more, young neurosurgeons are leaving teaching centers to establish themselves in communities less oriented in the diagnosis of neurosurgical diseases. At first, the impact of one upon the other may be slightly disconcerting to both. Open, sincere and friendly criticism, however, should soon dispel any misunderstandings, and the experience should be very educational for all concerned. It is with this in mind that I have prepared reports on a group of cases which have come to my attention in the first three years of practice in "virgin territory."

Redlich, Dunsmore and Brody[1] have called attention to several sources of error which the practitioner will do well to keep in mind. In a smaller community, the problems are similar but not exactly the same. First is the great popularity of the psychiatric diagnosis (or shall we now say "psychosomatic"?). Second is the lack of "brain tumor consciousness" or orientation in the neurosurgical field. Third is a deep skepticism as to the efficacy of neurosurgical technics and an attitude of "why bother to diagnose, you can't do anything anyway." Fourth is the improper use, or no use at all, of such readily available and easily used instruments of diagnosis as the skull x-ray, ophthalmoscope, tangent screen, caloric tests of equilibrium and chemical examination of the spinal fluid.

Redlich, Dunsmore and Brody[1] have given an excellent analysis of errors found in a university center and a review of the literature. It is not within the province of this paper to attack the problem in so scholarly a manner, but rather to present a few representative cases.

Foremost among the impediments to early care of neurosurgical diseases is the easy popularity of the psychiatric diagnosis, supported in the public mind by a constant barrage of emphasis from magazines, books and now the motion picture. This is the hardest to combat. The possibility of error is well illustrated by the following cases.

Case Reports

Case 1—A white, married woman in her early twenties first appeared for examination because of a twitching of the right corner of the mouth and dull, progressively severe headaches. Eighteen months before examination, she was delivered of her first baby. Immediately thereafter, she developed symptoms

FIGURE 1 *(Case 1)*. Angiogram of large meningioma.

which caused her family physician to send her to a psychiatrist with a diagnosis of postpartum psychoneurosis. At that time, she heard voices and saw bright lights. It was at that time, also, that her headaches began. There was no nausea, unsteadiness, weakness or paresthesia. After two consultations with the psychiatrist she was considered sufficiently improved to discontinue treatment.

At her first visit here, she still seemed to have visual and auditory hallucinations. Neurologic examination was singularly unrewarding. There was no impairment of the visual fields. The right fundus showed minimal elevation of the disk—1 or 2 diopters—with slight blurring of the disk edges and minimal congestion of the veins.

The spinal fluid pressure was at the upper limits of normal. The spinal fluid protein was 55 mg. per cent; the Wassermann test was negative; the gold curve was flat. Roentgenograms of the skull were also within normal limits.

A carotid angiogram revealed a large mass in the right middle fossa, evidently beneath the temporal lobe. At operation this proved to be a huge meningioma about the size of a large lemon (Figure 1). It was completely removed.

The patient made an uneventful recovery and, following operation, lost all her auditory and visual hallucinations and her headaches. At last examination she appeared to be symptom-free and there were no further convulsive movements.

This case illustrates how easy it is to be misled by a group of circumstances which fall into a certain pattern suggesting a psychiatric disorder. Here, pregnancy followed by visual and auditory hallucinations—in a woman having a first baby far from home under lonely circumstances—seemed to justify a diagnosis of psychoneurosis.

Case 2—A 73 year old woman was admitted to the hospital because of speech impairment, weakness of the right half of the body and impairment of memory. Two months before admission she had fallen and had received a head injury with momentary unconsciousness. This was followed by a period of mental depression and intermittent headaches. She was seen by her family physician who called in a psychiatrist. It was nearing Christmas and, for the first time in her life, she was not to have her family with her. After questioning her, the psychiatrist felt that this was a simple depression and treated her accordingly.

Approximately 10 days before admission the headaches became much more severe. Four days before admission the patient suddenly developed convulsive movements of the right arm, aphasia and paralysis of the right half of the body. Her temperature at this time was 100° F., pulse 121, respiration 20 and blood pressure 140/80.

Examination showed the typical signs of upper motor neuron impairment on the right side of the body, with positive Babinski's sign, increased deep tendon reflexes and no superficial reflexes. A carotid angiogram showed an enormous subdural hematoma on the left side (Figure 2). This was removed at operation.

Case 3—A 45 year old white man was

admitted to the hospital following a motorcycle accident. He had fractures of the left shoulder and upper arm and an injury to the radial nerve in the left arm. The neurosurgeon was called because of the radial nerve injury. During examination the patient suddenly stopped speaking, became semiconscious and developed a marked convulsive motion of the angle of the mouth on the right. Thirteen years before he had had a moderate head injury. Eight years before admission he had been hunting and had been found unconscious; about him were such evidences of violent movement as broken twigs, disarranged clothing, etc. Since that time he had had attacks of peculiar twitching in the right side of his face during which he was unable to speak.

Among his family and his neighbors he had recently developed a reputation for being a devil-may-care sort of person, although he held a very responsible position in a large corporation. The present accident had been the result of his effort to show his son that he could ride his new motorcycle, even though he had never ridden one and in spite of the fact that he knew he might be subject to an epileptic seizure of the face (as previously described) during the attempt.

A certain marked euphoria characterized his mental attitude. Although he was confined to bed with both arms disabled and had to be fed, and had rather frequent epileptic attacks of his face, his general mental outlook was that everything was quite all right and that he was having a good time. Because of this euphoria or *witzelsucht*, the facial convulsions, and the history of personality change, a carotid angiogram and a pneumoencephalogram were made. These showed a marked shift of the brain to the right and a mass in the frontotemporal area.

At operation a meningioma approximately the size of an orange was removed from the left frontotemporal area (Figure 3).

Sometimes, obscuring diseases or circumstances distort the findings. When this is the case, one must use every available device to arrive at a diagnosis, not excluding angiograms and ventriculograms.

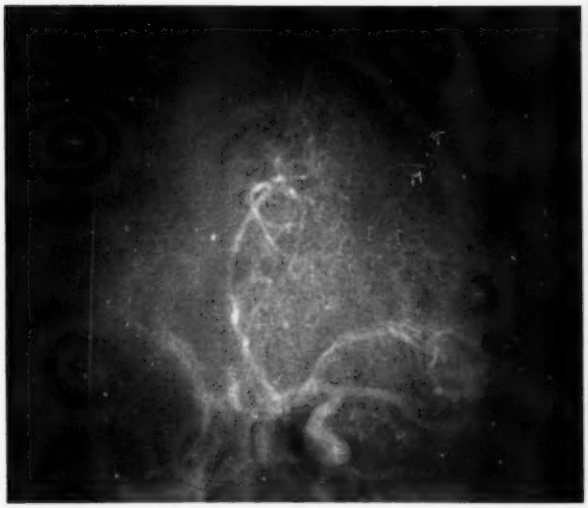

FIGURE 2 *(Case 2)*. Angiogram of large subdural hematoma.

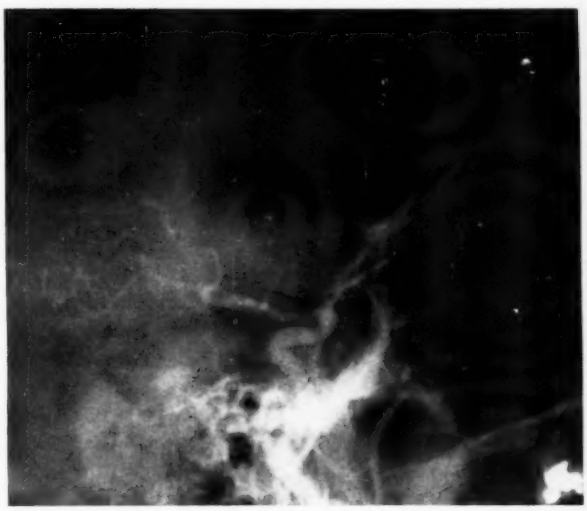

FIGURE 3 *(Case 3)*. Angiogram of sphenoid ridge of meningioma.

*Case 4**—A 27 year old white man was admitted to the hospital through emergency service because of a first convulsion. He had been hospitalized many times before for what

*To be published elsewhere as "Abscess of the brain secondary to pulmonary arterio-venous fistula."

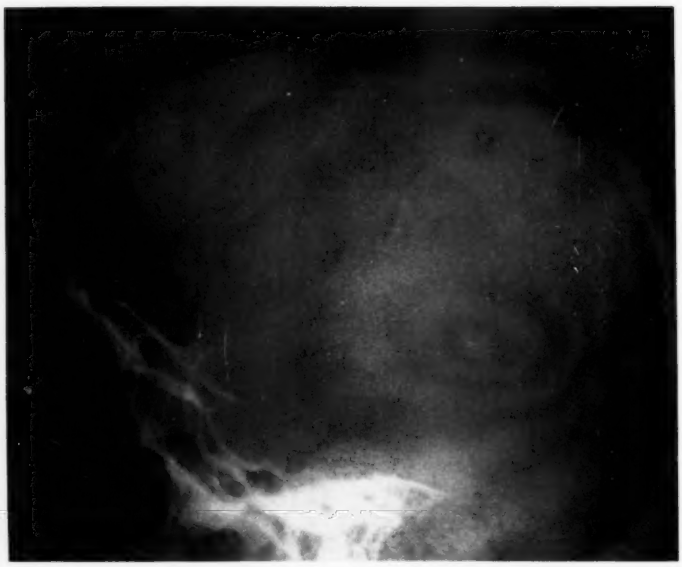

FIGURE 4 *(Case 6)*. Roentgenogram showing advanced erosion of sella due to pinealoma.

was diagnosed as secondary polycythemia on the basis of a congenital heart condition. He had a loud, blowing systolic murmur over the precordium. There was clubbing of the fingers. His red blood cell count on admission was 5,430,000 with 14 gm. hemoglobin, by the photoelectric method. The next day a direct count showed 8,440,000 red blood cells count and 12.9 gm. hemoglobin.

He had been complaining for some time of headaches and of paresthesias of one side of the body. For several hours after the convulsion he could not move his left arm, and some weakness persisted. There was minimal sagging of the left side of the face. A bilateral Babinski reflex was present. There was some blurring of the optic disks but no measurable papilledema. The spinal fluid showed no cells, 98 mg. per cent protein and 80 mg. per cent sugar. An air study was refused by the attending physician on the basis that this was a cerebral thrombosis due to polycythemia. The patient was discharged and sent home where he suddenly died during a convulsion.

Autopsy revealed a brain abscess of the right cerebral hemisphere and a pulmonary arteriovenous fistula.

Case 5—A 31 year old white man, who had had frontal sinusitis for many years, visited his physician, who tried to curet the frontal sinuses. Within a period of a few days thereafter the patient's wife observed that he began to change noticeably. He had always been meticulous about his appearance and a very careful driver. He was a salesman of tombstones and had always been very proper in his approaches. Now his manner became supercilious; he boasted of the huge profits he was going to make and drove about town at speeds faster than those prescribed by law.

There seemed to be gradual impairment of intelligence as well as untidiness, and he had increasing headaches. He was admitted to the hospital on two different occasions because of these symptoms and treated with antibiotics, the diagnosis remaining one of frontal sinusitis. Finally, the mental blunting became so marked that he became disoriented and did not respond well to simple commands. At this time a neurosurgeon was called. There was a left lower facial weakness, weakness of the left internal rectus of the eye, general mental obtundity, some blurring of the disk margins but no actual papilledema. It

was felt that because of the history of frontal sinusitis and the prominence of the personality changes there must be a lesion in the frontal lobe.

A carotid angiogram revealed a large mass in the left frontal lobe. At craniotomy a large brain abscess, both subdural and intracerebral, was encountered. This was evacuated and drained and the cavity washed out repeatedly with penicillin solution.

The patient made an uneventful recovery and regained his mental alertness and capacity. The abscess, however, had excavated most of the left frontal lobe. His euphoria and lack of restraint continued and have remained to the present time.

In one way, the neurosurgeon may be of benefit to his community by his mere presence, by his example of using the proper diagnostic instruments and by using them in the right way. It is surprising to find men who are very exacting in other fields still estimating spinal fluid pressure by the rate of the drip from the needle and ordering spinal fluid sugars when protein and gold curve would be more to the point. Where the ophthalmoscope and the perimetric examination are neglected, it is little wonder that headache, nausea and blurring of vision are more apt to suggest "gallbladder disease" than intracranial hypertension. More diagnoses are missed by not looking than not knowing, and this is especially true when roentgenographic studies of intracranial calcification, erosion of the sella and displacement of the pineal body indicate proper conclusions. The following case illustrates this point.

Case 6—A 48 year old man was admitted to the hospital because of frontal headache, dizziness, unsteadiness on his feet, diplopia, urinary urgency and occasional retention of four years' duration. He had had no nausea but he had had what he described as "blind staggers" during this whole four year period. Occasionally, he had fallen when going down steps or a steep bank. Once, when carrying his camera equipment (he was a professional photographer) across a street, he had had such a severe propulsion as to continue on through a plate glass window on the other side of the street.

During this period he had been hospitalized twice for possible gallbladder disease and had had tests and gastrointestinal x-rays both of these times. No one, however, had ever taken a skull plate.

On this last admission, four years after the onset of his symptoms, a skull plate was ordered and an erosion of the sella turcica was discovered so marked and of such long standing that it must certainly have been present for many years (Figure 4). There was no papilledema but there was failure of upward gaze. A huge pinealoma was found.

Summary

Cases have been presented which illustrate the mishaps and misconceptions in diagnosis of intracranial tumors found in a new practice of neurosurgery. The cases fall into four categories: (1) too great an emphasis on the psychiatric possibilities; (2) too little awareness of the possibility that a neurosurgical condition may exist; (3) a skepticism on the part of the patient or the doctor acting as an impediment to a sincere effort at diagnosis. and (4) failure to use or apply correctly easily used and readily available instruments of investigation.

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Fallacy in Allergy

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The diagnosis and treatment of allergic conditions is confused by fallacies. The basic errors underlie five additional fallacies. These must be abandoned and the underlying errors understood before the study of allergy can progress. The most devastating fallacy is that concerning the accuracy of skin testing. This concept results in erroneous diagnosis both of the allergic state and of offending allergens. Detection of allergens must be based on clues. The best of these come from the patient's experience, the next best from tabulation of the most frequent allergens, and the most inaccurate from skin testing.

ASHER A. WHITE

FROM the literature on allergy[1-4] an impression is gained of the operation of precise immunologic processes in the production of disease. Diagnostic procedures are envisioned, through the careful application of which a clear picture of the patient's sensitizations is acquired. It is then conceived that by an orderly process of elimination of or desensitization to these malefactors the patient will be restored to a condition free from allergic symptoms.

Despite the seeming clarity, when the physician applies these methods in the study of the allergic patient the expected results often fail to appear. As experience is gained, the student of allergy comes to realize more and more clearly that the methods employed in clinical allergy have serious shortcomings. The skin test is found to be unreliable, diagnosis of the allergic state uncertain, evaluation of the offending allergens difficult and desensitization frequently misapplied. The practice of allergy, even in the hands of the most expert, is found to be confused, empiric and contradictory.

Certain standard premises seem to underlie allergic methods. Skin testing is the diagnostic tool at most allergy centers; this implies a common belief that the skin test gives valid data. Allergic reactions are expected to follow known immunologic principles, and allergic diseases are regarded as easily diagnosed. Desensitization and elimination are the therapeutic tools of all. These principles and methods are regarded by each school as partially fallacious, but since no simple objective substitutes are available the fallacies tend to persist.

This exposition is an attempt to re-evaluate the known facts and to place fact and fallacy in perspective. It has proved difficult because of the several fallacies involved and the interdependence of each fallacy on the others. An

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attempt will be made here to select the fallacies, seek the reasons for their persistence, evaluate their results and review the facts with which they could be replaced.

By the turn of the last century hay fever and asthma had been observed to be concomitant so frequently that the etiologic identity of the two was recognized. Air-borne pollens had been demonstrated to be the cause of hay fever by some, as yet undefinable, mechanism. Information regarding anaphylaxis and immunity was growing apace. By 1910 many physicians were aware of the close similarity between the dyspnea of the anaphylactic guinea pig and the dyspnea of human asthma. The developing knowledge of anaphylactic sensitization provided the clue to the mechanism by which the asthmatic reaction occurred in certain persons following exposure to substances which for other persons were entirely innocuous. It was natural that human asthma and hay fever were considered analogous to the anaphylactic reactions seen in the experimental animal.

It was found in anaphylactic animals that injection of a minute amount of the sensitizing substance into the skin often produced marked whealing and erythema at the site of injection. With the recognition that hay fever was a disorder resulting from sensitization to pollen the experiment was made of applying the suspected pollen, usually grass or ragweed, to the skin of persons suffering from hay fever. The results were often dramatic, with large itching wheals and sometimes reproduction of the hay fever symptoms. At that time there was no intimate knowledge of pollination dates or amounts. Skin testing properly became a diagnostic tool and was the only diagnostic method available. It was inevitable that it came to be regarded as the *sine qua non* of allergic investigation—which position, despite its inaccuracies, it has held until recently. The successes achieved by recognition of hay fever as a manifestation of sensitization and by skin testing for evidence of that sensitization gave rise to two basic errors which seem innocuous but which underlie additional fallacies, the results of which have been devastating in some respects.

Terminology

To clarify the terms used, the following definitions are given:

Anaphylaxis—An immunologic phenomenon produced by reaction between a sensitizing substance and its specific antibody, the antibody being of a type demonstrable through circulating and cellular antibodies.

Allergy—An immunologic phenomenon presumed to be produced by reaction between a sensitizing substance and its specific antibody, the antibodies involved probably being of various types, often demonstrable through cellular antibodies, rarely through circulating antibodies and not infrequently undemonstrable by presently available technics. The so-called diseases of allergy (vasomotor rhinitis, asthma, hives, eczema and other less frequent reactions) are disorders in which allergy is but one among several possible etiologic factors. Each of the disorders may be produced by such diverse means as vegetative nervous overactivity, bacterial invasion, chemical trauma or mechanical trauma, as well as by the antigen-antibody reaction which is here called allergy. These disorders are most commonly seen in man, have only occasionally been demonstrated in animals and have been difficult to reproduce experimentally. This definition of allergy differs from another which is commonly employed wherein the term is used to signify any altered reactivity. Rhinologic and dermatologic literature is replete with instances in which the term is used to denote a tissue manifestation such as vasomotor rhinitis or eczema whether the etiology is an antigen-antibody reaction or another of the etiologic factors mentioned. In so using the term its immunologic connotation is lost.

Underlying Errors

1. Allergy is the human manifestation of anaphylaxis. Allergic disorders and anaphylactic reactions are in fact different facets of the biologic process which results in the production of antibodies. There are important differences in the behavior of the two phenomena which lead to fallacies of procedure when the behavior expected in anaphylactic

reactions is anticipated in human allergy.

The allergic disorders are characteristically found in humans (but in recent years have been recognized in some domesticated animals). Anaphylactic reactions were first recognized in laboratory animals and remain classic phenomena of the laboratory. They have, however, been recognized in human beings in such manifestations as serum sickness and serum shock. Allergic sensitization had not been produced artificially until very recently. The sensitization arises naturally in the course of ordinary exposure. Anaphylaxis is usually produced by artificial means such as a parenteral injection of sensitizing substance. The reaginic antibodies of allergic disease have been demonstrated only by tissue sensitivity. The anaphylactic antibody usually can be demonstrated in the test tube by precipitation or agglutination reactions. Anaphylactic reactions usually occur promptly on introduction of minute amounts of antigen. Allergic reactions usually develop more slowly and require large amounts of allergen.

The development of the fallacy already has been discussed, being principally occasioned by the recognition of the similarity of symptoms between the dyspnea of the anaphylactic guinea pig and the dyspnea of human asthma. As a result of the fallacy, allergic reactions are expected to be demonstrable in the same way as anaphylactic reactions. In the guinea pig sensitized to horse serum the injection of a small amount of the sensitizing serum into the skin gives rise in almost every instance to whealing and erythema. It is then expected that human skin injected with any substance to which the patient is allergic will respond with the same characteristic whealing reaction. In the anaphylactic guinea pig a minute dose of the sensitizing substance is all that is usually required to produce the anaphylactic reaction. It is therefore expected that in human allergy the symptoms will be produced by exposure to minute amounts of allergen.

To eradicate the fallacy, we must recognize that the immunologic process is a many-sided phenomenon, immunity to disease representing one facet, anaphylaxis another and allergy a third.

2. Accuracy of diagnosis in pollinosis is due to the accuracy of skin test data. The physician usually conceives that cause and effect relationships will be clearly manifest for other allergens, since they are clear in pollinosis. It is assumed that the accuracy is obtained by virtue of the accuracy of the skin test to pollen. When, however, the diagnostic methods in pollinosis are analyzed, it is found that it is not the accuracy of the skin test which makes diagnosis more accurate in pollinosis than in allergy to other agents. The skin test is no more accurate in pollinosis than in other allergic diseases. Many positive results are obtained to pollens appearing in the air at times when the patient has no symptoms. Many negative reactions are obtained to pollens which are determined by other means to be symptom-producing.

The accuracy obtainable in pollen diagnosis depends on the correlation between the dates during which the patient's symptoms occur and the dates of pollination for each plant. The pollination dates of wind-pollinated plants have been thoroughly studied.[5-10] Each such plant begins producing pollen on almost the same date each year and terminates its pollination at a later date which varies little from one year to the next. Thus, in Minnesota grass pollen is in the air in abundance from Decoration Day until the end of June, and ragweed pollen from about August 5 to September 15. When symptoms appear in a given patient each year from Decoration Day to the end of June or from the first week in August to mid-September, it is obvious by correlation with the pollination dates that diagnosis can be made with some assurance without the use of skin tests. It has not been realized that the accuracy of pollen diagnosis is due less to skin test results than to the exact knowledge of the degree and time of exposure to pollens, knowledge which is seldom clearly ascertainable in symptoms produced by other allergens.

Additional Fallacies

1. Allergy is easily demonstrated. It is hazily conceived by both physician and layman that the diagnosis of an allergic state can be made with facility and that etiologic

allergens can be diagnosed with certainty. The truth is that in a high percentage of allergic patients, cause and effect relationships are not determined even after the most expert search. The fallacy derives from other fallacies discussed, such as the belief that skin testing accurately reveals allergic sensitization, and the concept that reactions of allergy are as clearly reproducible as those of anaphylaxis.

Difficulty in eradicating the fallacy is encountered because the clinician has been furnished an entrancing explanation for allergic phenomena. There is sufficient proved truth in these explanations to suggest that the whole fabric of allergic practice is based on reasonable grounds. When the orderly system of skin testing and desensitization does not work as clearly in practice as in theory, the physician nevertheless carries out these methods to the best of his ability according to the dictates of his conscience. When diagnostic failure occurs he is confused and insecure.

To replace the fallacy certain facts must be recognized. Immunity, anaphylaxis and allergy are phenomena which are only partly understood. Reagin or skin-reacting antibody is demonstrable in certain allergic patients, but in others poorly understood conditions can becloud its demonstration either by causing reagin to fail to exhibit itself when present or by causing skin reactions which falsely simulate it. The clarity of diagnosis obtainable in pollen allergy cannot be as easily attained with other allergens. The only proof of allergy is reproduction of the symptom on exposure to an allergen.

2. *Skin tests are accurate indicators of allergic reactivity.* The error of this premise is revealed in the observations that the degree of skin reaction at test sites will vary both with repeated control tests (nonantigenic material) and with repeated testing with the same antigenic extract. When the control test solution is applied intradermally at several different sites on the ventral surface of the subject's forearm, the reactions 20 to 30 minutes after application may vary from no reaction to reactions of edema and erythema as broad as 1 cm. to occasionally 2 cm. in diameter. In other words the reactions may vary from 0 to 1 plus and rarely to 2 plus. The significance of this observation is simply that skin reacts in the same way to various stimuli. The reaction resulting from antigen-antibody union cannot be differentiated from the reaction resulting from the trauma of scratch or intradermal injection.

This is the most devastating of the fallacies commonly held regarding allergy. It arose because the early work in allergy was with hay fever, where accuracy in diagnosis of etiologic pollens is usually attainable. The accuracy is due to correlation between data obtained from three sources: the dates of occurrence of symptoms, the dates and amount of pollination for each wind-pollinated plant, and the results of pollen skin tests. For sensitizing agents other than pollens we usually lack knowledge of the exact time and amount of exposure. It can seldom be determined with precision just how much exposure has taken place, nor is there rhythmic recurrence of symptoms to correlate the known times of exposure. In order to attain accuracy in diagnosis we must supply by planned exposure the two correlating factors: degree of contact and time of appearance of symptoms.

Fallacious conclusions are drawn as a result of the belief that skin tests afford accurate data. The presence of a positive skin test is believed to demonstrate the presence of allergic disease. Substances resulting in positive skin tests are expected to be the cause of symptoms. Thus the presence or absence of allergic disease is erroneously diagnosed, as are the etiologic agents. Eradication of the fallacy is difficult because skin testing affords the only simple objective method of obtaining information regarding sensitization in a given patient.

To replace the mistaken notion of the accuracy of skin testing, several facts must be kept in mind. The immediate skin reaction to test substances is not an accurate indicator of reaginic activity. A positive skin test does not signify that the patient is a victim of an allergic symptom nor that the substance causing the positive test will produce an allergic reaction. Substances producing positive skin reactions frequently cause no symptoms after

exposure. A positive skin test must be regarded as no more than a clue, the validity of which remains to be determined. The patient who shows no positive skin tests is not necessarily free of allergic disorder. Symptom-producing allergens frequently evoke no skin response. With air-borne pollens, compensation for the inaccuracy of skin testing is obtained by exact knowledge of degree and time of exposure to such pollens, so that diagnosis in pollen allergy becomes reasonably simple whereas diagnosis of allergy to other agents is confused and uncertain.

3. Manifestations of allergy are pathognomonic. The untruth of this premise is seen in the observation that symptoms and signs indistinguishable from those of allergy can be shown to be due to infection and to emotional reactions. The fallacy persists because of loose definition of terms. The physician recognizes that infection and emotion may induce symptoms identical to allergy. It is common practice to use the term allergy to describe these symptoms without regard to their etiologic origin. The term should be restricted to symptoms presumed to be produced by antigen-antibody reactions. The unfortunate result of this looseness in use of the term allergy is that patients with syndromes due to causes unrelated to immune mechanisms are skin tested for reagin and are given desensitizing injections to substances having no relation to the symptoms. Acceptance of more rigorous definition will help to restore a measure of validity to allergic study.

4. Small doses of antigen suffice to induce allergic symptoms. The error of this premise may be seen clearly in certain observations. In individuals sensitive to foods the patients' experience often indicates that they will tolerate a considerable quantity of antigenic food before symptoms occur. When, however, an excessive amount of that food is ingested, symptoms develop. The requirement of large doses of allergen for symptom production is also seen in pollinosis. The plant giving rise to the etiologic pollen usually has been producing it in moderately high atmospheric content for several days before the patient's symptoms develop.

There are reasons for the persistence of this erroneous premise. First, many case histories indicate that minute doses of certain antigens may be symptom-producing. These dramatic reactions becloud the realization that these cases are the exception rather than the rule. Second, the anaphylactic reaction usually is accomplished with minute doses of antigen. By analogy, the conclusion is drawn that the same must hold for allergic phenomena.

As a result of this error in concept, inadequate methods of trial by exposure are used in evaluating allergic patients. In provocative feeding, for instance, a small serving of the suspected food usually is offered. Experience indicates that in persons sensitized to a certain food it may require three or four days of excessive feeding of that food before symptoms appear.

5. Desensitization will protect against inhalants giving rise to positive skin tests. Desensitization is a satisfactory procedure against inhalants to which allergy has developed. The fallacy consists of regarding skin tests as affording accurate evidence of sensitization. As commonly practiced, the diagnosis of allergic agents depends on skin testing and is therefore seriously inaccurate. From the results of skin tests a diagnosis is made of sensitization to bacteria, to fungi, to house dust or to other agents. Having arrived at a diagnosis based on false evidence, the fallacious conclusion is reached that desensitization to agents so diagnosed will be effective. The conclusion is strengthened because desensitization was first used in pollinosis, where it was satisfactorily effective. Its effectiveness was dependent on accuracy in diagnosis of offending pollens. It was erroneously conceived that the accuracy of diagnosis thus attained was due to the accuracy of skin testing. The physician is further tempted to use desensitization against inhalants which cannot be removed from the environment because no other method of therapy is available. As a result many patients receive desensitizing injections to substances to which they are not allergic. Eradication of the error is difficult, because recognition of the inadequacy of the skin test has been slow and because other

therapeutic methods have had no spectacular success. It must be recognized that skin test results are not sufficiently accurate to base desensitization procedures on them.

Areas of Ignorance

The fallacious concepts discussed could not exist if our knowledge concerning the allergic mechanism were adequate. There are several areas which need illumination.

It is known that allergic phenomena are antigen-antibody reactions. The way in which they differ from the parent phenomena of immunity and anaphylaxis has as yet no answer nor has the question as to whether allergy and immunity are due to the same antibodies. It is not known whether allergy develops as a result of normal conditions of exposure or whether it occurs only under abnormal circumstances. There have been various speculations: that allergy occurs only in individuals who are physiologically abnormal; that it occurs only in persons and families who possess a genetic abnormality, or that there may be required for its development a deficiency or excess of factors such as vitamins, minerals or other metabolites.

Three types of phenomena from sensitizing antibody are recognized: (1) those from the reaginic type of antibody, (2) those from the anaphylactic type of antibody and (3) those from the tuberculin-reacting type of antibody. It is possible that sensitizing antibodies other than these are formed and give rise to some of the clinical phenomena observed in allergy. In so-called intrinsic allergy of infection, for instance, none of the known types of antibody has been demonstrated to be the cause of the manifestations.

An understanding of the chemistry of allergic reactivity of different types might improve allergic therapy. On the basis of the concept that histamine mediates the phenomena resulting from reagin-producing or wheal-producing antibodies, antihistaminic drugs have been developed. They are, however, unsuccessful in asthma, suggesting that some substance other than histamine may be active in bronchial allergy. Allied to the chemistry of the allergic state is the chemistry involved in the functional or emotional phenomena which frequently simulate so closely allergic reactions. Knowledge of the chemistry of these phenomena is needed.

One of the greatest needs is for an accurate means of determining when allergy is present and to what substances sensitization has occurred. When the validity of the skin test is denied as a means of determining the presence of the allergic state we find ourselves most inadequately equipped to determine whether allergy is present. When the skin test cannot tell us with certainty the substances to which antibody has been developed, the clinician is left with a difficult problem of detection as to which substances are the chief offenders. Many methods of diagnosis have been hopefully evaluated because of recognition of the inadequacy of skin testing. Leukopenic indexes, eosinophilic indexes, mucous membrane testing, both nasal and anal, and attempts to improve the quality of skin test substances all have met with scant success.

Fallacies Must Be Abandoned

The first requirement for the physician dealing with allergic patients is to abandon the fallacious ideas which have for so long obscured the subject. Randolph[11,12] recently suggested that because of its errors, skin testing to foods should be entirely abandoned. The physician would thus be freed from the direction of misleading guideposts. It is my opinion that it is not necessary or advisable to abandon the skin test completely; rather, its inaccuracy must be recognized and the physician's thinking reoriented.

In accepting the invalidity of skin test data the physician must also accept the obscurity of present knowledge in the allergic field. When the skin test is used only as a clue, the whole false structure founded on the validity of the skin test falls apart. It becomes apparent that the diagnosis of the presence of allergy is insecure, that desensitization injections must not be instituted until proof of the cause of symptoms is attained, and that elimination diets must be based only on the evidence obtained by the feeding and elimination of single foods. A vast body of puzzling and

repetitious investigation in allergy has for years been based on the assumption that the skin test accurately reflects the presence of reagin in the body. Denial of this premise throws into discard much of such evidence, but by closing the fallacious avenue of investigation it leaves the field open for new research along more fruitful lines.

Alternative Methods

It is unproductive to be critical of present fallacies without replacing the methods based on these errors with alternative methods of procedure. When skin test reactions are given the status of clues instead of facts, diagnosis of the allergic state will depend on other data which are unfortunately indirect and supposititious. The most direct evidence of the allergic state is gained from the patient's experience. A clearcut relationship between alteration in symptoms and changes in food or dust exposure is the most positive evidence available. A past history of other symptoms which are frankly allergic in origin is helpful in recognizing patients who are constitutionally susceptible to allergy. Minor additional evidence is had from blood eosinophil counts, sedimentation rate, eosinophils in nasal or bronchial mucus and from a family history of allergy.

Patients who by these means give evidence of an allergic state may then be studied for diagnosis of the offending allergens. The most important clues in this evaluation will again be the patient's experience regarding the development of symptoms when exposed to inhalants or foods. As a second source of clues, skin testing may now be performed. Positive results, however, may not be regarded as proof of the presence of reagin in the skin; rather, they should be considered questionable evidence which may be validated in the final analysis only by the production of symptoms on exposure to that substance or invalidated by a contrary result. A third source of clues as to possible offending agents is obtained by listing in order of frequency those substances causing known symptoms in allergic persons. Certain foods and inhalants are commonly etiologic in allergic illness, while others are rarely so. Those which commonly act as allergens may be regarded as more likely sources of sensitization in the patient who is under study.

Desensitization has great value in pollinosis and almost as great value in protecting against certain ubiquitous inhalants such as house dust and molds. When we have ceased to base desensitization on results of skin tests we will use desensitization only where the relationship between an inhalant and the symptoms has been proved by other means.

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Neurosurgical Clinic

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This is a case of an intracranial lesion which presented an unusual panorama of symptoms at the onset, which in turn offered a nice problem in differential diagnosis.

I AM going to report on a case which has come to my attention recently. The patient has not been brought here today, for reasons which will become obvious as the report progresses.

W. JAMES GARDNER

This patient is a 50 year old woman complaining of failing vision. She is the attractive wife of a professional man, and has been subject to migraine attacks all her life. These attacks have gradually increased in frequency over the years, and at present they occur about every two weeks.

The first warning of an attack is a blurring of vision in the left eye. Sometimes if she takes an APC® capsule it may develop no further than that. However, in a full-blown attack the blurring of vision in the left eye lasts from a few minutes to 30 minutes, and this is followed by scintillating scotomas in the right eye and then by headache. This headache usually begins in the left frontal region, spreads to involve at times the entire head, and ends up on the right side. In a severe attack the headache lasts until she goes to bed at night and it is gone when she awakens in the morning. The next day, as is usual in patients with migraine, she feels quite washed out and tired.

On August 25, 1952, this patient noticed the usual blurring of vision in the left eye preliminary to an attack. The onset was a little unusual, however, in that for the first time this blurring was followed by bilateral scintillating scotomas. Ordinarily the latter were confined to the right field of vision, but on this occasion both fields were involved. This was followed by headache accompanied by vomiting. It was a severe headache, but not essentially different from her usual severe attacks.

She awakened the next morning feeling fagged out, as usual. She was not too keen in her observations, but by the following day when she again felt normal she noticed that the blurring of vision in the left eye continued; it seemed as if there was a black spot in front of the eye. This persisted, and three weeks after this episode she went to an ophthalmologist. He found that the visual acuity was 6/7.5 in the right eye and down to 6/15 in the left eye. Perimetric fields were normal for form, but in the left eye there was a complete temporal hemianopsia for red. The color field was normal in the right eye.

Four weeks after the onset of her trouble she again consulted the ophthalmologist, who studied her visual fields once more and found

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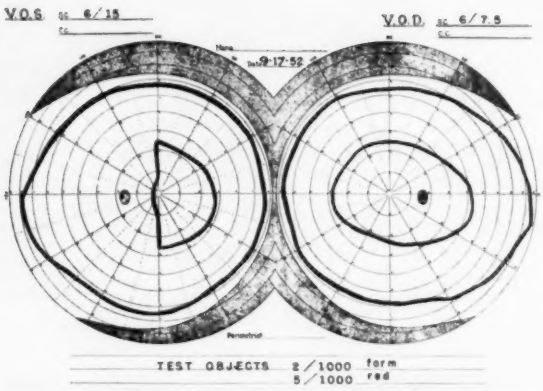

FIGURE 1. Visual fields three weeks after onset. The larger circle represents the form field, and the smaller the field for red appreciation. There is a temporal defect for red in the left eye only.

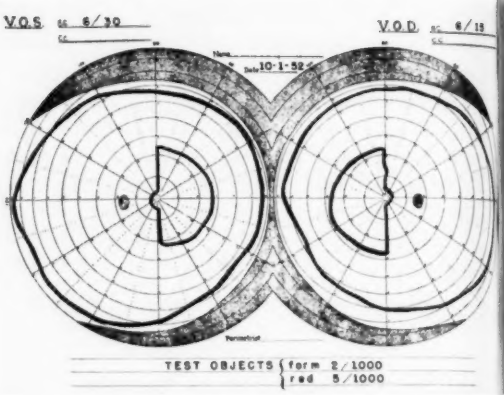

FIGURE 2. Visual fields five weeks after onset. Temporal hemianopsia for red has now become bilateral. Visual acuity is reduced in both eyes.

that the temporal defect for red was now present in both eyes. The visual acuity had come down to 6/15 in the right eye and 6/30 in the left eye. The patient began to notice a tendency for letters to run together and she avoided reading. There was also some photophobia, which had not been present before, except perhaps during her headaches.

Her husband noticed that there was slight instability in walking, but the patient attributed this to some sedative which she had been taking.

Six weeks after the severe migraine attack which initiated these symptoms, excessive thirst developed suddenly and she began to pass large quantities of urine. This has continued to date; in other words, she had, in addition to a lesion of the optic chiasm, diabetes insipidus.

The patient became aware of further visual loss nine weeks after the onset. When she reported for her weekly eye examination, the bitemporal hemianopsia for color had become complete also for form.

The patient readily admits that she has always been nervous and tense and that by nature she is a perfectionist. She keeps an immaculate house, and because of her thoroughness and capabilities she has been secretary of a ladies' auxiliary for many years. She has, in short, the type of personality which is found so often in persons subject to migraine.

She is also subject to arthritis, and two years ago she had a shoulder-hand syndrome on the right side with Sudeck's atrophy, additional evidence of autonomic imbalance. A hysterectomy was performed in 1939, and she is still having some menopausal symptoms for which she is taking estrogens. Her blood pressure has generally been subnormal.

The neurologic examination in this case, 11 weeks after the onset of symptoms, disclosed no findings except the bitemporal hemianopsia. The patient was of normal habitus and did not appear ill. She was alert, described her symptoms accurately and exhibited a normal degree of concern regarding them. The blood pressure was 108/75.

Let us go back to the first eye examination eight weeks ago and three weeks after the onset. You will recall that at that time there was a loss of appreciation for red in the temporal field of the left eye only. That is very unusual. When a visual field defect is confined to one eye it indicates that the lesion is in the retina or optic nerve. It is very difficult to explain a unilateral field defect on the basis of an intracranial lesion. It should in-

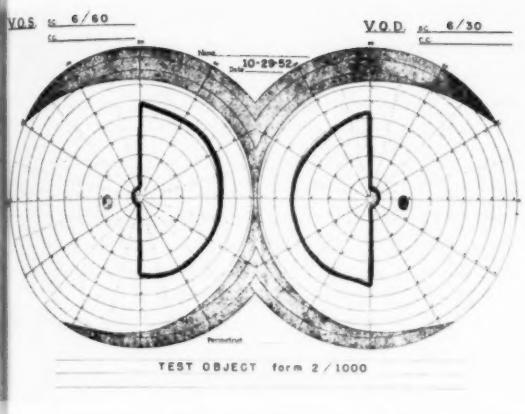

FIGURE 3. Visual fields nine weeks after onset. Patient is now unable to recognize red and has a bitemporal hemianopsia for form. Visual acuity is still further reduced in both eyes.

volve symmetric parts of the fields of both eyes if it is a cerebral lesion.

You will further recall that this patient's attack of migraine was ushered in by the usual blurring of vision in the left eye. The unusual feature was that it was still present three weeks later.

The auras of migraine are vasospastic in origin and the vasospasm may affect any of the branches of the internal carotid artery. The ophthalmic artery is one of the branches of the internal carotid artery and supplies the retina which is, so to speak, a part of the brain. Until this point it appeared likely that this patient's visual difficulty which came on with this attack of migraine and persisted for three weeks probably was due to ischemic damage to the retina resulting from the spasm of the retinal vessels. However, a couple of weeks later the visual fields showed that the defect for red which had been present only in the temporal field of the left eye now involved also the temporal field of the right eye. Furthermore the reduction in visual acuity which had been confined to the left eye was now present in both eyes.

At this point it became obvious that the lesion must be intracranial and at the level of the optic chiasm, the only place where a single lesion could produce this picture.

A couple of weeks later, as you recall, the bitemporal hemianopsia which had been present only for appreciation of red became complete for form also, so that she was unable to recognize a white object as well as a red one in either temporal field. By this time it was quite obvious that the symptoms were not due to vasospasm.

Roentgenograms of the skull disclosed no definite findings. The roentgenologist felt that there was possibly some narrowing of the anterior clinoid process on the left side and that this might indicate a lesion above the process, but it was a slight change and not definitely pathologic.

The patient was apprehensive and expressed the feeling that if she had an operation she would not survive. For this reason action was deferred until it became obvious that the lesion was definitely progressing, and, of course, no mention of surgical intervention was made.

This patient has now entered the hospital for further study.

In summary, therefore, we have a middle-aged woman who has had migraine all her life, occurring on an average of twice a month; she has always had a tendency to have low blood pressure, which I think is significant; she had one of her usual attacks 10 weeks ago, following which the visual aura persisted; this blurring of vision was found to be due to a temporal defect for appreciation of red in the left eye and then in both eyes; it then went on to a complete bitemporal hemianopsia, followed by the development of diabetes insipidus. From this steady march of symptoms there can be no question but that there is an expanding lesion compressing the region of the optic chiasm and the third ventricle.

Bitemporal hemianopsia always means a surgical lesion. On the other hand, a homonymous defect, i.e., where it is the right half of each retina or the left half of each retina that is blind, is produced by any lesion which interrupts the optic tract or radiation. The lesion can be anywhere posterior to the optic chiasm, from there back to the occipital cortex. But when the visual field defect is a

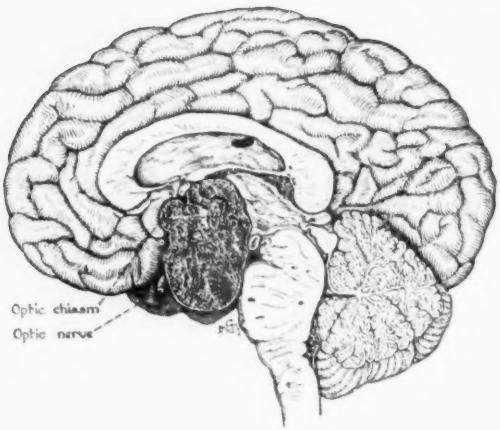

FIGURE 4. Pituitary adenoma representing the most frequent cause of bitemporal hemianopsia. Note the tremendous dislocation of the optic chiasm with resultant stretching of the optic nerves occasioned by these growths. This tumor arises below and behind the optic chiasm.

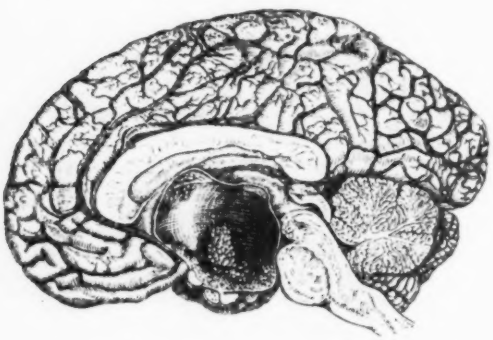

FIGURE 5. The craniopharyngioma, a frequent cause of diabetes insipidus. This tumor arises as a rule above and behind the optic chiasm.

This patient underwent surgery on November 11, 1952, at which time a right frontal craniotomy was performed and a tumor disclosed beneath the optic chiasm. A biopsy revealed carcinoma. Subsequently a lump was found in the breast. Preoperative roentgenograms of the chest were negative. The patient's course was progressively downhill and she died on November 29, 1952. Postmortem examination disclosed carcinoma of the right breast, undifferentiated type; secondary carcinoma of the brain; multiple, regional lymph nodes and adrenal; moderate emphysema, and congestion of the liver, spleen and kidneys.

Metastatic carcinoma of the hypophyseal stock and optic chiasm is a rare condition. It was not suspected in this case.

bitemporal hemianopsia, the lesion is a discrete one. It is in the optic chiasm and it is produced by pressure; it is *never* the result of a stroke or vascular spasm or hemorrhage or thrombosis or any of the other nonsurgical lesions which might produce a homonymous field defect.

The auras of migraine, as I stated, are due to vasoconstriction of the branches of the internal carotid artery. The headache itself, as has been pointed out so ably by Wolff, is the result of vasodilation, which affects chiefly the extracranial vessels but sometimes the intracranial vessels also. These two phases of the migraine attack do not overlap. There is the vasospastic phase, which consists of the aura; then the vasodilator headache phase occurs.

The auras of migraine are most commonly visual; if not, there may be a feeling of numbness, aphasia, scintillating scotoma with flashing lights, or a homonymous hemianopsia, but never a bitemporal hemianopsia. Occasionally the impairment of vision due to the vasospasm may be confined to one eye due to spasm of the retinal artery.

It has been shown in the cases of migraine with auras consisting of homonymous field defects or scintillating scotoma that there are changes in the electroencephalogram over the corresponding occipital cortex. That this is due to vasospasm is demonstrated by Wolff, who showed that the aura of migraine can be relieved transiently at least by the inhalation of amyl nitrate.

Migraine attacks, even in persons without evidence of diffuse or local vascular disease, occasionally may precipitate intracranial vascular accidents. These accidents are the result of changes in the caliber of the vessels that occur during the aura and also during the headache phase, and the lesion itself may be an intravascular thrombus or an extravascular hemorrhage.

Migraine attacks, therefore, are instances of a completely reversible disorder of function, which, however, may induce irreversible tissue damage. In this case, in view of the location and progressive nature of the lesion it could not be considered an aftermath of

the migraine attack. We therefore had to consider other possibilities and particularly intracranial lesions which are known to be associated with migraine.

When a person with migraine develops sudden symptoms of intracranial organic pathology, one must always think of the possibility of an associated berry aneurysm on the circle of Willis. The incidence of berry aneurysm in patients with migraine is at least two or three times as high as it is in the general population.

Berry aneurysm is so-called because it looks like a berry. It is about the size of a small berry and has a narrow stalk corresponding to a stem.

The migraine attack, however, is not produced by the aneurysm. Rather it represents an anatomic anomaly which is associated with the physiologic anomaly which expresses itself in the migraine attack. For instance, when a patient with migraine is found to have a berry aneurysm, the aneurysm may just as well be on the side opposite the side of the headache as on the same side.

There are other conditions in which berry aneurysms are associated, notably coarctation of the aorta and polycystic kidney disease. Berry aneurysm is a congenital anomaly; at least it is due to a congenital weakness of the blood vessel wall which leads to this outpouching. It is not part of generalized vascular disease or hypertension.

In addition to this patient's bitemporal hemianopsia you recall she developed diabetes insipidus. The pituitary gland, as you know, consists of two portions: the anterior lobe, which is the glandular portion, and the posterior lobe, which is the neurohypophysis. The anterior lobe is the master gland of the human body, which exerts its influence on all the other endocrine glands. It is formed from an outpouching from the primitive nasopharynx and is epithelial in its structure. The posterior lobe, or the neurohypophysis, consists of a small portion located posteriorly; it is of nervous tissue, and together with the pituitary stalk and a small prominence—the median eminence—just above the pituitary stalk in the hypothalamus, it controls water metabolism.

When a lesion affects the posterior lobe of the pituitary gland, if it also includes the other portions—the stalk of the gland and the median eminence of the hypothalamus—the patient develops diabetes insipidus because of a lack of formation of the antidiuretic hormone which is produced in the neurohypophysis. The patient with diabetes insipidus does not urinate large quantities because he drinks a lot; he drinks a lot because the fluid is not held back in the kidneys and his tissue fluids become depleted and that creates an excessive thirst.

Lesions which produce diabetes insipidus and, for that matter, bitemporal hemianopsia, are always located above the sella turcica. A lesion within the sella turcica cannot produce either of these because the structures responsible—namely, the median eminence, the pituitary stalk and optic chiasm—are located well above the sella turcica.

Let's consider the diagnostic possibilities in this case. Despite the negative roentgenogram and despite the fact that the onset occurred during an attack of migraine, we know from the steady progression of her symptoms and their nature that she has an expanding lesion above the sella turcica. What are the possibilities? One of the most common lesions in this region is an adenoma of the pituitary gland. However, this nearly always erodes the sella turcica and almost never causes diabetes insipidus. Pituitary adenomas are of two varieties: the chromophobe type which produces evidence of hypopituitarism, and the acidophilic type which produces the typical picture of acromegaly. The patient exhibits no evidence of either of these conditions.

A pituitary adenoma may be a very large lesion, but despite its size, it almost never produces diabetes insipidus.

The type of tumor which is most apt to produce diabetes insipidus is the craniopharyngioma or Rathke's pouch cyst. This tumor results from a congenital cell rest. Rathke's pouch is the outpouching of the primitive nasopharynx which goes to form the anterior lobe. Sometimes a remnant of that remains, and it may not produce symptoms until middle life. It is an epithelial-lined cyst

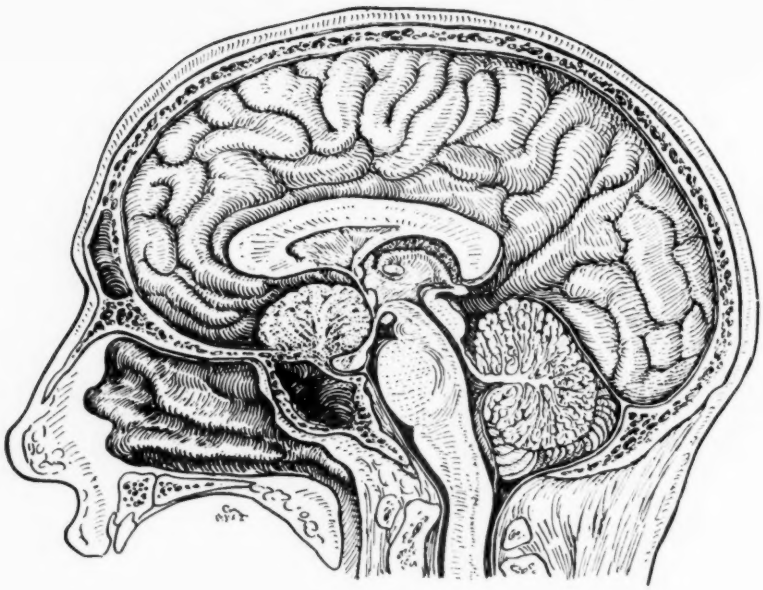

FIGURE 6. The suprasellar meningioma. This tumor arises from the base of the skull in front of the hypophysis and optic chiasm, and rarely causes bitemporal hemianopsia or diabetes insipidus. (Figures 4, 5 and 6 from Bailey, Percival: Intracranial Tumors. Springfield, Illinois, Charles C Thomas, 1933.)

which contains cholesterin crystals and fluid and desquamated epithelium, and it usually compresses and destroys the hypophyseal stalk and also compresses the third ventricle. In that way it interrupts the neurohypophyseal function and leads to diabetes insipidus.

Another type of lesion which is occasionally found is the suprasellar meningioma, which arises in front of the sella turcica and compresses the gland and the chiasm. However, it does not produce diabetes insipidus because it is located in front and does not damage the particular area which is essential to the development of diabetes insipidus.

What are the possibilities, or at least what is the most likely possibility, in this woman's case? We can exclude a vascular accident resulting from a migraine attack because this is a progressive lesion; furthermore, it is in the optic chiasm and not in the visual cortex. We believe that the onset at the time of the migraine attack may have been coincidental. By the way, she hasn't had an attack of migraine since.

Going into her history, we find that she has always had low blood pressure. A lesion compressing the hypophyseal stalk, as pointed out by Cushing 30 years ago, invariably produces hypotension. Therefore we may suspect that there was a lesion in the hypophyseal stalk before she developed these recent symptoms. I think that the most likely diagnosis is craniopharyngioma or Rathke's pouch cyst. Perhaps in the vasospastic or vasodilator phase of this last attack of migraine, a rupture of a vessel occurred into this cyst, with the resulting expansion of the cyst so that it is now producing symptoms, whereas before this the only evidence of it was low blood pressure.

I doubt very much that this is a berry aneurysm because a berry aneurysm may occur above the optic chiasm or along the optic tract but almost never occurs beneath the optic chiasm.

The treatment in this case will be to make a carotid arteriogram in order to rule out the possibility of aneurysm, and then to proceed with surgical exploration of this area.

NOTE: A few days after the foregoing presentation, this patient was operated on and a suprasellar tumor found which proved to be metastatic from an unsuspected carcinoma of the breast.

Papilloma of the Bladder

WILLIAM J. ENGEL*

Cleveland Clinic, Cleveland, Ohio

The pedunculated papillary tumors of the bladder (papilloma) should be separated from other bladder tumors in selection of treatment and prognosis. They behave more like benign tumors. Biopsy examination may be useful, but careful cystoscopic evaluation supplemented by intravenous urography is of greater importance in proper recognition and selection of treatment. Complete local excision and destruction by transurethral resection or through suprapubic cystotomy afford excellent results. Careful follow-up is essential to long-term success.

WILLIAM J. ENGEL

I HAVE been guided by two considerations in selecting my subject for this clinic: (1) I believe this type of bladder tumor should be considered separately, and (2) it is my opinion that conservative treatment yields excellent results.

In recent years there has been a tendency to consider all bladder tumors as carcinoma and to separate them only on the basis of histologic grading. To consider all tumors as carcinoma may provoke a sense of hopelessness and, more importantly, may cause the surgeon to adopt more radical measures than may be necessary. The main objection to grading tumors is that it places the responsibility for treatment in the hands of the pathologist, whereas in fact the decision as to type of treatment should rest with the clinician and particularly with the cystoscopist. It is my feeling that the cystoscopic examination of the bladder is in many respects more important in the decision as to treatment than histologic grading. By that I don't mean it isn't important to know the results of biopsy; rather, the grading of a tumor must fit with the cystoscopic appearance of the tumor in the final selection of treatment.

Clinically, all epithelial tumors can be divided into two groups: (1) papillary tumors which grow into the cavity of the bladder, and (2) solid tumors which have a tendency to grow into the wall of the bladder, invading deeply and occasionally even extending beyond the wall.

As Jewett and others have pointed out, the degree of infiltration is as important—if not more so—as the histologic grading in estimating the prognosis from surgical treatment.

Cystoscopic Characteristics

1. Papilloma of the bladder is a superficial tumor which grows into the cavity of the bladder.

2. It has soft, villous, finger-like projections, although the villi may coalesce, giving a rather solid appearance to the tumor.

3. There is no evidence of bladder wall in-

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Presented before the thirty-seventh annual Assembly of the Interstate Postgraduate Medical Association at Cleveland.

vasion—i.e., adjacent mucosa appears normal.

In larger tumors there is a bushy overhanging margin, and this is important. The attachment is narrower than the tumor; thus they are pedunculated tumors—they hang like grapes on a stem. They may be multiple; if so, each has the same characteristics and the intervening mucosa is normal. Generally speaking, about half are single and half are multiple.

Usually no ulceration is present. The bladder capacity generally is normal. The most common sites of involvement are the trigone and floor of the bladder adjacent to the trigone.

Differentiation must be made between the papillary tumors and the more solid types. In the latter, the tumor extends down into the bladder, and ulceration is common.

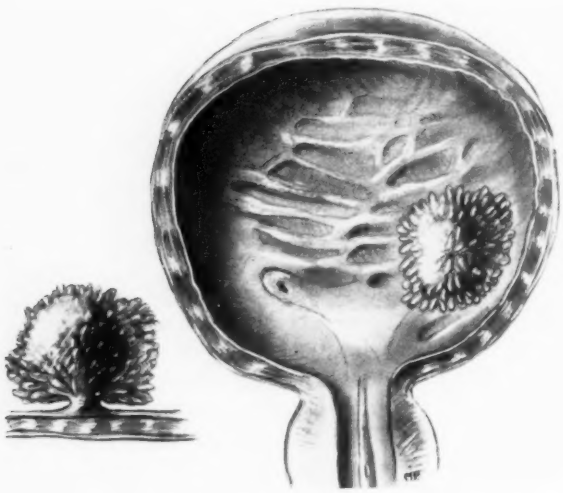


FIGURE 1. Semidiagrammatic drawing showing the appearance of a pedunculated papilloma of the bladder.

Symptomatology

The cardinal symptom, hematuria, occurs in 96 per cent of the cases. It is typically painless and intermittent. The patient may observe blood in a single specimen of urine, following which he will have no such symptom for one or two months or even six months. Because it stops so promptly, it often is regarded as of no significance, and the patient does not seek medical help.

Typically there is no dysuria, frequency or pyuria, because the capacity of the bladder is not diminished and there is no ulceration. Between attacks of hematuria the urine may be essentially normal except for an occasional red blood cell.

Diagnosis

Cystoscopic examination is the most important diagnostic method. Intravenous urography is exceedingly valuable, and with this method it can be determined whether there is any ureteral obstruction. The presence of ureteral obstruction is an indication of an infiltrating tumor; its absence is evidence of a pedunculated, nonobstructive, noninfiltrative type of tumor.

It is very important that you do serial cystograms. We take them at intervals of 5, 15, 30 and 60 minutes. The importance of serial study is evident—if you take a cystogram only at the end of an hour, the bladder may be so full that it obscures the tumor.

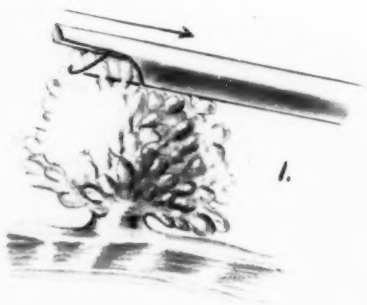


FIGURE 2 *(right)*. Drawings showing some of the maneuvers employed in the operation of transurethral resection of bladder papilloma. The object is to expose the narrow pedicle, which is then divided. This may be accomplished by either advancing or withdrawing the loop, as circumstances dictate.

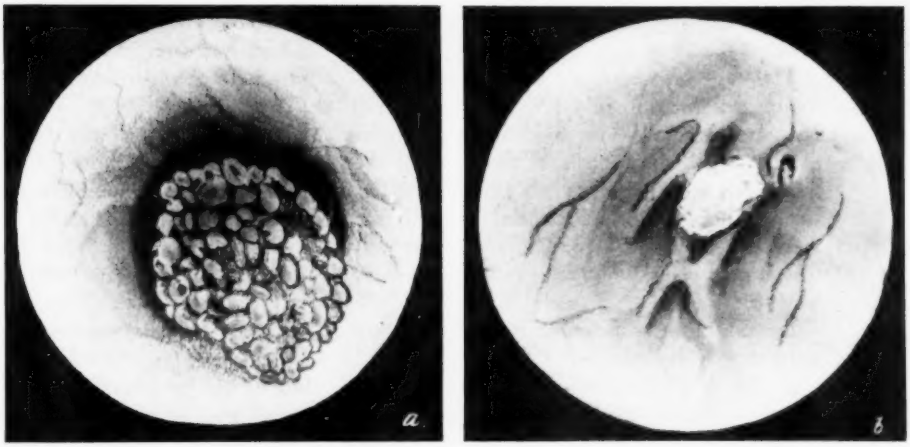


FIGURE 3a. Cystoscopic view of papilloma of the bladder before removal. b. Cystoscopic view after removal of tumor. Note small area of base in contrast to size of tumor. Also note the proximity to the ureteral orifice.

Illustrations from Engel, W. J.: Transurethral excision of papilloma of the bladder. S. Clin. North America, October 1937. Reproduced courtesy W. B. Saunders Company.

Treatment

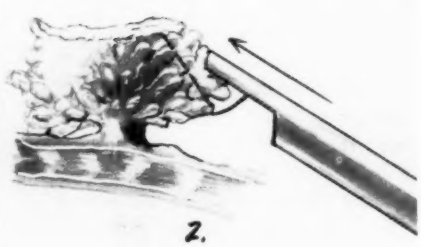
The patients I shall describe illustrate certain features of treatment.

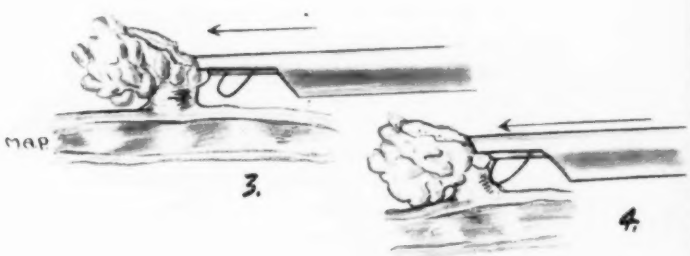
Case 1—I first saw this young woman in August 1934. At that time she had a four month history of intermittent hematuria. For two weeks prior to her visit she had had an extremely severe bout of hematuria which was continuous and which had resulted in secondary anemia.

Cystoscopic examination disclosed the presence of a small pedunculated tumor of the bladder, not much larger than a grape, which was bleeding from one of the vessels in the terminal villi. A transurethral resection of the tumor was done. This woman has returned regularly for cystoscopic investigation for 18 years, and there has been no recurrence of the tumor.

This case represents treatment by means of simple transurethral excision, and about 25 per cent of tumors that you remove will not recur. This is particularly true of single tumors.

Case 2—A 29 year old man was seen in January 1948. He had had an attack of hematuria and had consulted his physician. A cystoscopic examination had been done and a biopsy made. Between the cystoscopy and the biopsy the surgeon had recommended total cystectomy. Additional opinion was sought. It was then that I saw the patient. At cystoscopic examination we found a tumor on the left side of the bladder which was definitely a





pedunculated type. It measured 4 cm. in its greatest diameter.

The surgeon who had done the first cystoscopic examination in this case also had put in some radium seeds, and except for some edema and telangiectasis at the base of the tumor we felt there was no evidence of invasion. Transurethral resection was advised and carried out. The pathologic report was transitional cell carcinoma, grade 2, papillary in type.

I think a brief account of his follow-up visits will be instructive.

In March 1948 he returned and there was still the radiation ulcer as a result of radium, but no evidence of recurrence of the tumor. In May 1948 one minute papilloma was noted on the right side—mind you, this was the opposite side of the bladder. The radiation ulcer had not yet completely healed. In August 1948 the ulcer appeared to be healed. There were three small papillomas on the opposite side of the bladder, and these were fulgurated. In December 1948 one small new tumor was observed on the right lateral wall, and this was fulgurated. In April 1949 three new small tumors were treated. In August 1949 a tumor the size of a cherry pit was removed by transurethral resection with the loop. In December 1949 no recurrence was noted. In September 1950 a tumor the size of a grape seed was observed on the dome of the bladder. In January 1951 three pinhead-size lesions were electrocoagulated.

The interesting feature of this case is that in July 1951 cystoscopic examination was entirely negative, and in January 1952 there again was no evidence of recurrence.

I wish to point out that the bladder that grows one tumor can grow another, and it may be in a completely different location. Perhaps these new tumors should not be called recurrences.

Case 3—A man first seen in November 1951 had experienced hematuria several weeks previously, but it had been associated with symptoms of severe cystitis and it was presumed that the two conditions were related. However, hematuria recurred, and a cystoscopic examination showed an extremely large tumor of the bladder. A tremendous filling defect was seen in the bladder, but there was no ureteral obstruction. We considered this tumor to be a bushy overhanging pedunculated type of papilloma. Conditions prevented removing the tumor by the transurethral route, so it was done by suprapubic cystotomy. A huge pedunculated tumor larger than a baseball was removed, together with several others in the adjacent area. The total weight of the tumor was 135 gm. Electrocoagulation of the bases of the tumors was done.

This operation was performed in November 1951. In January 1952 he returned for cystoscopic examination, and three prepapillomatous lesions were noted and electrocoagulated. At present there is no sign of any new tumors.

Case 4—This woman was first seen in July 1945 by my former chief, Dr. Lower. She complained of hematuria and symptoms of frequency and urgency of urination. Cystoscopic examination showed the presence of multiple tumors, and there was evidence of ulceration and encrustation of these tumors. Transurethral resection was done in July 1945. For the next two years the problem became one of attempting to control the multiple recurrences. There literally were tumors all over the bladder.

In 1946 we tried deep roentgen ray therapy, with little improvement resulting. In my experience deep therapy and radium have been of limited or no value in treatment of persons with papillomas of the bladder. Tumors appeared so rapidly that we elected to do a bilateral ureteral transplantation and a total cystectomy. On August 20, 1947, I did a bilateral ureterosigmoidostomy, and on October 14 a total cystectomy by a combined vaginoabdominal approach.

An intravenous urogram taken about 10 months after operation shows essentially normal kidney pelves.

Cystectomy will not often be required, but occasionally in a case in which recurrences are so rapid that they cannot be controlled by conservative measures, the operation becomes necessary. If it is done, the outlook should be good because these tumors are

neither invasive nor infiltrative. If you remove the entire bladder the chance of tumor formation is certainly minimal.

Case 1 represents the result which may be expected in about 25 per cent of cases of papilloma of the bladder. Case 2, in which there were some recurrences, represents about 50 per cent. In other words, new tumors can be expected in about half the cases.

Prior to 1941, open operation was done in 39.7 per cent of the patients with papillomas that were treated. Since 1941 only 10.2 per cent have been treated by means of open operation. This may be the result of earlier diagnosis, but it also may be due to the fact that as one becomes more familiar with the possibilities of transurethral excision, more and more patients can be treated in this manner.

Technic of Transurethral Excision

Briefly the technic of transurethral excision by means of the resectoscope is: In very small tumors the pedicle may be simply divided with the loop, thus removing the tumor in one bite. The base and adjacent mucosa are then electrocoagulated. In larger tumors one cannot see the pedicle and so must remove the tumor in such a way as to expose the pedicle. You can take it off from the top or from the front, and finally get down to where the pedicle can be seen. Then it is divided by pushing the loop forward or, in many instances, pulling the loop back.

Summary of Management

The first treatment is the most important, and this depends on recognition of the true nature of the tumor. This is accomplished by careful cystoscopic examination, biopsy and intravenous urography.

Complete local removal is adequate treatment. Rarely, rapid multiple recurrence requires cystectomy.

Radium and roentgen ray therapy have limited if any value in treatment.

It is exceedingly important to conduct very careful follow-up studies on these patients. We urge them to return in six weeks; if there is no new tumor at that time we ask them to return in three months, then in six months and then every year. If there are new tumors at any examination, we return more or less to the original schedule.

Less than 10 per cent of these papillomas progress to frank invasive malignancy. In my series of cases the percentage was 5.7; in Dr. Kretschmer's it was 7. In this connection it is interesting to recall that in the heterologous transplant studies which Dr. Green carried on in New Haven, he has shown considerable evidence that transplantation is dependent on the malignancy of the tumor. They have not been able to do a heterologous transplant in these papillomas of the bladder.

MEETINGS AND POSTGRADUATE COURSES

International Academy of Proctology: Fifth annual convention, May 29-31, at the Plaza Hotel, New York City, directly preceding the American Medical Association meeting. There is no attendance fee. Programs are available on request to the Executive Offices of the Academy, 43-55 Kissena Boulevard, Flushing, New York.

University of Minnesota, Minneapolis: Continuation course in electrocardiography, June 8-12, for general physicians, with emphasis on practical experience in interpretation of electrocardiograms.

University of Southern California: Graduate course in gastroenterology, beginning September 1953 and continuing through August 1954. Course is designed to give training in basic sciences and clinical studies in this field. Dr. George K. Wharton will be in charge.

Surgery in Poliomyelitis in Infancy and Childhood

WILLIAM T. MUSTARD*

Children's Hospital, Toronto, Ontario

Convalescent care of poliomyelitis in infancy and childhood is more difficult than it is in older children and in adults. Deformities develop quickly and progress with growth. The orthopedic surgeon must be constantly on the alert for deformities which can be corrected by soft tissue operations. These operations include division of fasciae, division of deforming muscles, transfers and tenodesis. Stabilization operations in older children are more satisfactory in the absence of gross deformities.

I WILL confine my remarks to surgical procedures for children with poliomyelitis and will not discuss those for persons in older age groups. The indications for and the timing of operations of a soft tissue nature, e.g., division of tensor fasciae, tendon transfer and tenodesis, can, I think, be outlined best by describing 2 little patients who were brought here from Rainbow Hospital through the courtesy of Dr. Stanley Hoerr. Douglas and Mary both had poliomyelitis four months ago. Beginning with the boy, I will describe briefly the various procedures which would be done if some of his paralysis persisted.

W. T. MUSTARD

Upper Extremity

Douglas' right arm is in fairly good condition and the prognosis would be excellent. There is classic weakness of the deltoid but this is not marked, and the function probably will improve. There is some flexor weakness of the elbow, but no operative procedure is indicated. In his hand there is classic deformity of the opponens and an excellent example of lack of apposition of the thumb. It is very important that children regain the power of apposition as quickly as possible, and we do an opponens transfer four, five or six months after poliomyelitis. I would do a transfer in this case immediately, and the function of his whole hand would improve.

He has some additional weakness in his hand. When he makes a fist, the hand goes up in hyperextension because of the weakness of the flexors of the wrist. There also is weakness of the sublimis tendons, and one would have to consider which to use as a transfer. Another important point demonstrated in this case is involvement of the opponens muscle, a common finding in poliomyelitis. If there is no abductor or a weak abductor, the opponens transfer does not produce satisfactory results, so you must reroute the long extensor as it passes around the tubercle, and bring it over to make an abductor of it. In my experience it has to be brought over a great deal farther than would be expected. I bring it over as far as the flexor carpi radialis and make a little loop out of that tendon before doing the opponens transfer.

Mary, the other little patient, is 9 years old,

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Presented before the thirty-seventh annual Assembly of the Interstate Postgraduate Medical Association at Cleveland.

and was in a respirator during her attack of poliomyelitis. She has a perfectly good arm and her opponens muscle functions well. She has a poor deltoid, but this is not significant at this stage (four months post-polio). I would predict that the deltoid will be functional. If there was absence of function of the deltoid at this stage, then it would be likely that this muscle would not regain function. In Mary's case consideration should be given to a shoulder fusion, the only operation about the shoulder, in my opinion, that is successful. To do a shoulder fusion, one must have two good muscles: (1) a trapezius and (2) a serratus. The procedure must not be done before the age of 10 years, not because of bone growth but because of lack of bone. In children less than 10 years old you would be dealing almost entirely with cartilage and you would have nothing to fuse by the time you got the cartilage away.

A second procedure I shall mention is flexoplasty of the elbow. Neither of these children demonstrates enough weakness to warrant this. Douglas has considerable flexor weakness, and unfortunately it can be predicted that he will have a lot more. If the weakness present now (four months post-polio) were evident a year or two after polio, I would certainly consider doing a flexoplasty of the elbow.

Another procedure done on the upper extremity early in childhood is transfer of the wrist flexor to a finger extensor.

Spine

The spine in poliomyelitis is one of our big bugbears. Mary demonstrates weak abdominal muscles. One should watch carefully for a deviation of the umbilicus to one side, when attempting to get these children into a sitting position, because that means inequality of the abdominal musculature and indicates subsequent development of scoliosis. Mary already has a slight curve. She is still fairly stiff, but this curve will have to be observed very closely, because with growth it will increase.

I wish someone would tell me what to do about such a curve when it develops in a child after poliomyelitis, because it is long and sweeping and progresses rapidly with growth. Because of its nature, fusion should not be done for a child less than 10 years old; a large segment would have to be fused and this would interfere with growth. We carry these children along in plaster jackets, put them to bed if necessary for a while, stretch them, and so on. I don't think physiotherapy does anything to a scoliosis resulting from polio except perhaps increase it a little.

Lower Extremity

The first important consideration in the lower extremity is the possibility of a flexion-abduction contracture of the thigh. This condition is easy to detect in infancy; the affected leg is a little longer than the other. The cause, of course, is abduction contracture at the hip, the iliotibial band. It is an insidious and particularly deforming condition, and one must be on the lookout for it.

When examination discloses that one leg is longer than the other, look for hip flexion deformity. Dividing the tensor right down through the intramuscular septum, placing the child in a cast and pulling on the opposite leg will prevent other deformities that may ensue from a tight iliotibial band, e.g., knock knee, pelvic obliquity. I have done this in infants as early as two months post-polio. One reason infants are more likely to develop this deformity than patients of older age groups is the diaper, and I call it a diaper deformity.

The important muscle about the hip is the abductor, the gluteus medius. When Douglas stands on his right leg he drops way over to the side, indicating weakness of the abductor on the right. In the presence of an abductor lurch and a positive Trendelenburg sign, one examines for abductor power. One trick is not to bring the leg too far forward, for in that case the sartorius comes in and also the tensor. I would rate the abductor not any better than a trace in Douglas' case, and at four months post-polio that is a serious rating for this particular muscle, and is characteristic of no return of power.

For this disability the only thing you can do is transfer of the iliopsoas. The iliopsoas frequently escapes when the abductors are

FIGURE 1. Progressive tilting of os calcis due to weak calf.

involved. This is because of a difference in the anterior horn cells. The sartorius, which must have good function if you take away the iliopsoas, also often escapes involvement. We bring the iliopsoas out through the pelvis and put it below the greater trochanter on the opposite side. Results in cases in which this procedure has been done have been very satisfactory, and I am particularly pleased with them because it is my operation.

The practical procedure for the knee is the hamstring transfer forward. This should not be done in childhood; as a matter of fact, I think it is done far too often in all age groups.

Mary has a lot of weakness in her legs, and a weak triceps muscle on one side. If she were to have to handle crutches, it would be rather difficult. We like to roll the brachioradialis over to assist the triceps for crutch walking, and that works very satisfactorily.

She has bilateral quadriceps involvement and probably will benefit by a transfer when she is older. The semitendinosus and biceps are good. Transfer should not be done until she is about 12 years of age. With a nil quadriceps and a strong hamstring one might expect flexion deformity to develop, so one should watch that carefully and if necessary hospitalize the child and stretch the knee to 130 degrees, because a flexion deformity is difficult to handle.

Foot

The first consideration in regard to the foot is the calf muscle. In Douglas' case, the calf muscles are weak. To test for such involvement, hold the os calcis in your hand, because if you merely get the child to push the foot down, everything else is pushing too. He should be able to pull the os calcis right out of your hand. Douglas can do this on one side, but on the other he has very little calf muscle, a serious finding at four months postpolio. We feel it is very important to prevent

the calcaneus deformity, i.e., the rotation of the os calcis (Figure 1). The foreshortening of the foot is a serious disability and the calcaneus gait is poor. We do a transfer back to the heel very early, and I would do it right now in this case—take the posterior tibialis and peroneus longus and put them into the os calcis. In this way rotation of the os calcis and foreshortening of the foot will be prevented.

What can we do if there is nothing to transfer to the heel? In the past there was nothing that could be done except ankle fusion. You can't do an ankle fusion before the age of 12 or 13 years, so we have revived Dr. Gallie's operation, tenodesis of the achilles tendon (Figure 2). In order to hold the heel we cut the tendon and put it into the tibia to act as a check rein to prevent the heel from rotating. This procedure has been done in a lot of these cases, and I think it should be used in this particular group of children. Later, ankle fusion can be done if necessary. An equinus deformity is far better than a calcaneus one.

Mary demonstrates the reverse situation. She has no anterior tibial on one side. This is a very strong muscle, and its absence will result very quickly in an equinus deformity. When she starts to walk you can see the cock-up of the great toe and valgus of the foot, and I would do a transfer very early. I would take the peronei and put them in the dorsum of the foot, which would take away the deforming quality of the peroneus longus and reduce the equinus development.

Summary

Deformities develop very quickly in childhood, and must be prevented rather than repaired after they have developed. There are only a few operations of choice. In the upper extremity the transfers about the hand, particularly the opponens transfers, should in my opinion be done early—six months post-polio. Flexoplasty of the elbow can be done in a year, not taking any bone. In the lower extremity about the hip, divide the tensor early. In abductor weakness, transfer the iliopsoas laterally but not for two years post-polio. In my opinion transfer should never be done about the knee in childhood. About the foot, transfers are very important. Transfer to the heel if there are tendons available. Transfer to the heel if there is weakness or absence of calf muscle. If there is nothing transferable to the heel and a nil calf muscle, do posterior tenodesis. Do a transfer of the peronei to the dorsum in an anterior tibial weakness. Don't fuse the interphalangeal joint in childhood.

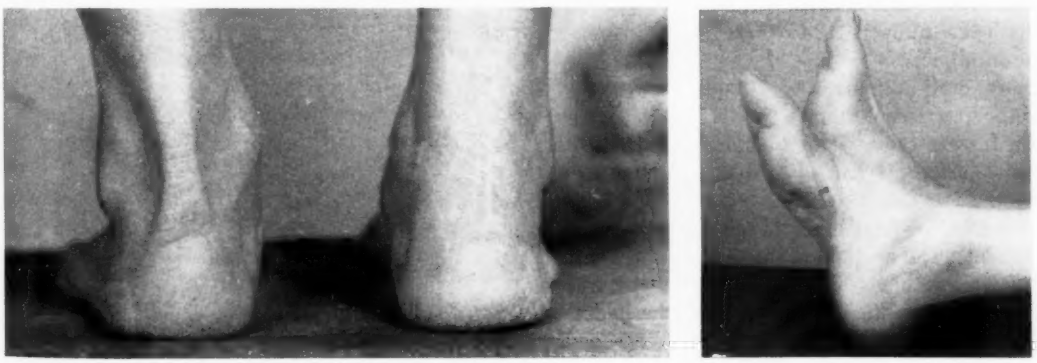

FIGURE 2a and b. Tenodesis of the achilles tendon, 16 years postoperatively.

A New Approach to Increasing Tolerance to Oral Aminophylline

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AND J. STANTON KING, JR.*

Bristol, Tennessee, and New Orleans, Louisiana

A new approach to increasing tolerance to oral aminophylline therapy is reported. It consists of giving, together with aminophylline, a nonabsorbable, sodium-free antacid in the form of aluminum hydroxide gel. This mixture greatly reduces the irritating effect of aminophylline on the gastrointestinal tract without interfering with its absorption. It permits the administration of larger doses of aminophylline for therapeutic purposes.

GEORG CRONHEIM

T. T. JUSTICE, JR.

J. S. KING, JR.

THEOPHYLLINE, although it has proved to be an effective diuretic, has not been administered extensively in oral form for this purpose because of the undesirable side effects such as nausea and vomiting which accompany oral administration. In a recent study by Justice, et al.[1] it was demonstrated that a daily dose of 1 gm. of oral theophylline can produce a diuretic effect, but that this dose could be tolerated only by about half of the patients. The available evidence indicates that the emetic effect is principally due to free theophylline which is liberated by the hydrochloric acid in the stomach. Side effects may be avoided to some extent by administering theophylline in enteric-coated tablets. However, due to variations in the breakdown of the coating, the results are erratic.

Krantz, et al.[2] approached this problem by combining theophylline with a soluble buffer of sodium glycinate. Since this preparation provides about 12 mg. of sodium for each 100 mg. of theophylline, it is contraindicated for many patients who need theophylline therapy. The same applies to the use of sodium bicarbonate in adequate amounts.

In this present study, aminophylline (theophylline ethylenediamine) has been combined with a nonabsorbable, sodium-free antacid in the form of aluminum hydroxide gel. Theophylline blood level determinations were recorded and tolerance studies were conducted in normal individuals. The results of high doses of oral aminophylline in clinical therapy will be reported by Adams.[3]

It was first demonstrated by theophylline blood levels that aluminum hydroxide gel did not interfere with absorption of theo-

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TABLE 1

THEOPHYLLINE BLOOD LEVELS FOLLOWING ORAL ADMINISTRATION OF AMINOPHYLLINE*

(26 CONVALESCENT HOSPITALIZED PATIENTS)

	THEOPHYLLINE BLOOD LEVELS (MG./100 CC.)	
	Without aluminum hydroxide gel	*With aluminum hydroxide gel*
2 hours after first dose	0.69	0.54
2 hours after fifth to eighth dose	0.73	0.71
2 hours after last dose	0.65	0.66
14 hours after last dose	0.29	

*Two groups of 13 patients each. One group received only aminophylline (3 gr. every eight hours for four to five days); the second group received 3 gr. of aminophylline plus 4 gr. of aluminum hydroxide gel.

phylline from the gastrointestinal tract. Theophylline blood levels were determined at timed intervals in 26 convalescent hospitalized patients (Table 1). One group of 13 patients received 3 gr. of aminophylline plus 4 gr. of aluminum hydroxide gel every eight hours. This amount of aluminum hydroxide gel neutralizes approximately 100 cc. of 1/10 normal hydrochloric acid. It represents about twice the total acidity found in the normal fasting stomach and about the upper limit of acidity after an Ewald test meal. The second group of 13 patients received only aminophylline. The experiment extended over a period of five days. Three blood samples were taken—one each after the first, fifth to eighth, and the last (thirteenth to fifteenth) dose. Each sample was taken two hours following oral administration of the drug. In 9 of the patients it was considered advisable to take an additional blood sample 14 hours after the last dose. The theophylline content of the plasma was determined according to the method of Schack and Waxler.[4]

The data in Table 1 indicate that the theophylline blood levels are the same in both groups. Thus, it can be concluded that the simultaneous oral administration of aluminum hydroxide gel does not interfere with the absorption of theophylline from the gastrointestinal tract when the latter is given in the form of aminophylline. It is interesting to note that in all 9 patients where a blood sample was taken 14 hours after the last dose, appreciable theophylline blood levels were still present. The figures in Table 1 concur with those reported previously for aminophylline and other theophylline components.

After it had been established that aluminum hydroxide gel had no effect on the theophylline absorption and blood levels, the effect of this antacid on the gastric tolerance of aminophylline was studied. Fifteen hospitalized patients each received 6 gr. of aminophylline plus 12 gr. of aluminum hydroxide gel every four hours. This dosage schedule was followed for a period of from six to eight days. The aminophylline was given in the form of uncoated tablets and the aluminum hydroxide gel as 3 per cent aqueous suspension.

Eleven of the 15 patients tolerated the large dose of 36 gr. of aminophylline per day without any difficulty. In the remaining 4, medication was discontinued due to severe nausea and/or vomiting. In addition to the 4 instances of gastric disturbances, 1 patient with emphysema developed frank tachycardia which disappeared promptly on cessation of the drug. In several of the patients a slight increase in the heart rate was observed.

The dose of 36 gr. of aminophylline administered daily in this test corresponds to 28.8 gr. (1.86 gm.) of theophylline per day. If one considers that a daily dose of 9 to 12 gr. of aminophylline (0.46 to 0.62 gm. of theophylline) in the form of uncoated tablets frequently exceeds the tolerance limit, the amount given patients in this test represents a three to fourfold increase of medication.

From our own studies[1] we can supply the following data. In 26 acute tolerance tests, a daily dose of 0.96 gm. of theophylline (1.2 gm. aminophylline) produced nausea or vomiting in 50 per cent of the patients. When daily doses of 0.64 gm. of theophylline (0.8 gm. aminophylline) were administered to 37 patients for therapeutic trials, the incidence of nausea reached 42 per cent.

In the present study, after simultaneous administration of a daily dose of 1.86 gm. of theophylline with aluminum hydroxide, nau-

sea or vomiting occurred in only 27 per cent of the patients. Even though the dose of aminophylline was increased from two to three times, the incidence of gastric disturbances was reduced from 50 to 27 per cent.

Increase in heart rate was not considered a contraindication to large doses of aminophylline. On the contrary, it is thought that perhaps the increased amounts of aminophylline which can be given in combination with hydroxide gel will permit a more reliable and rational use of aminophylline as a cardiovascular drug.

Discussion

This study shows that when aminophylline is combined with aluminum hydroxide gel large oral doses of the drug can be tolerated. The combination of these drugs makes it possible to administer theophylline in larger amounts without the disadvantages encountered in other methods of administration. This applies particularly to the use of enteric-coated tablets or rectal suppositories where absorption varies,[7] and where therapeutic results are frequently unreliable. With regard to other commonly used methods of administration, intramuscular injections are very painful, while intravenous injections often cause undesirable side reactions due to the high initial theophylline blood levels. Furthermore, intravenous injections are required at least once every day which is obviously not practical for patients having chronic heart disease.

In combination with aluminum hydroxide gel, aminophylline is well tolerated by most patients in doses varying from 1.0 to 1.6 gm. (15 to 24 gr.) per day; it has been shown that this amount is sufficient to produce a reliable diuretic effect.[1] In many instances, the daily dose of aminophylline can be increased to even larger amounts as indicated in the aforementioned test series where 11 out of 15 patients tolerated 36 gr. of aminophylline per day.

Thus, it may be possible to give aminophylline by the oral route in amounts sufficient to obtain the cardiac-stimulating effect demonstrated after parenteral administration.[5] This belief is also supported by the observation that "the increased cardiac output following the administration of aminophylline is associated with the higher concentrations of the drug found in the blood."[6] Following parenteral administration of 0.5 gm. of aminophylline, Waxler and Schack[7] found theophylline blood levels of 0.60 to 0.70 mg. per cent maintained over a period of about three hours. It has been shown in this and in a previous study[1] that such blood levels can be obtained easily with oral administration. Since the medication can be repeated at frequent intervals and the incidence of gastrointestinal side reactions is materially reduced by the use of aluminum hydroxide gel, effective blood levels can be maintained with oral medication not only for three hours but for any desired length of time.

Summary

1. Theophylline blood levels have been determined after aminophylline (theophylline ethylenediamine) has been given orally both with and without aluminum hydroxide gel.

2. The addition of aluminum hydroxide gel has no effect on the absorption of theophylline from the gastrointestinal tract as indicated by theophylline blood concentration.

3. Acute tolerance tests, extended over a period of five days, have shown that when aluminum hydroxide gel is administered with aminophylline the irritating effect of aminophylline on the gastrointestinal tract is greatly reduced; thus, large doses of aminophylline can be tolerated.

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CASE REPORT

Trilobectomy and Lingulectomy for Bronchiectasis

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A case of extensive, bilateral bronchiectasis treated by maximum resection of lung tissue is reported.

W. P. KLEITSCH

BRONCHIECTASIS is a benign disease curable by surgical operation. This is an important observation since the patient with untreated bronchiectasis, at best, can look forward to a short and unhappy life. Often the large amounts of foul-smelling sputum raised make him a social outcast, while the weakness associated with the chronic sepsis usually precludes gainful employment. Although medical treatment offers much in the control of sepsis and in the management of the constantly recurring pneumonitis, it cannot influence the anatomic defect of a dilated and diseased bronchus. For permanent cure of the condition, therefore, surgery is necessary. The fact that surgery is curative is even more encouraging in view of the fact that such operations now carry a risk (mortality rate) of less than 0.5 per cent.

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are a result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Almost all cases of bronchiectasis are amenable to surgical care. In rare cases the involvement of bronchi is so extensive that surgical resection would result in the sacrifice of an intolerable amount of pulmonary tissue. Ordinarily, pulmonary function is actually increased by resecting the diseased portion of lung; however, there is a point beyond which pulmonary reserve becomes compromised. As the pulmonary vascular bed is reduced in area, there is also a point where the resulting pulmonary hypertension begins to throw an excessive burden on the right side of the heart. Unfortunately an objective method for accurately determining these points is lacking. However, available pulmonary function tests, together with careful clinical appraisal, permit a fairly adequate preoperative evaluation of the anticipated postoperative effects.

Although bronchiectasis usually involves the lower lobes of the lung, occasionally it may involve the upper lobes or even an entire lung. All combinations of anatomic involvement are possible. The case herein reported is one in which bronchiectasis involved both lower lobes, the middle lobe and the lingula. There was also evidence of some relatively minor involvement in the left upper lobe which did not become apparent until after

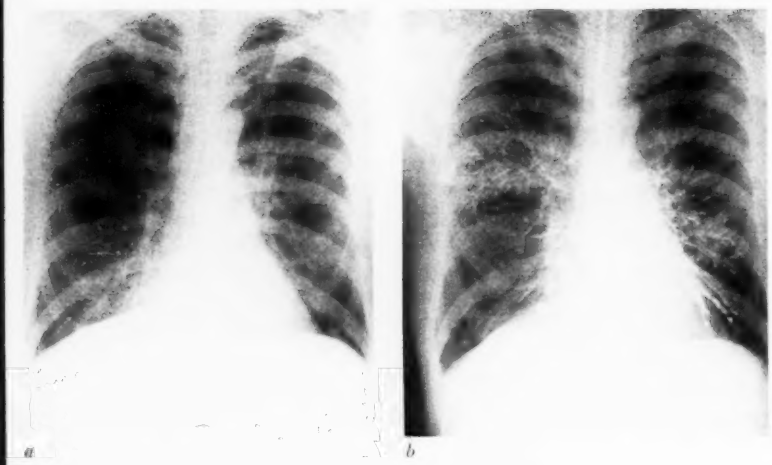

FIGURE 1. Preoperative x-rays of the chest. The routine film shows an increase in the basal markings on the right. The bronchogram shows extensive lower lobe bronchiectasis on the left and bronchiectasis and incomplete filling of the right lower and middle lobes.

operation. Excision of the diseased pulmonary tissue constituted what is probably a maximum resection.

Case Report

A 35 year old white man was admitted to the hospital September 21, 1950, complaining of a constant cough and excessive sputum. He had been well until four years previously when he had developed pneumonia, following which he had continued to expectorate large amounts of thick, purulent sputum. He had also become extremely weak so that he had been forced to abandon his occupation as a shipbuilder.

Results of the physical examination were entirely normal and a routine roentgenogram of the chest was also normal, there being no parenchymal infiltrations or nodules. A bronchogram on September 25 showed marked cylindric and saccular bronchiectasis in all the branches of the lower lobes on both sides and similar involvement of the lingula on the left and the middle lobe on the right, as illustrated in Figure 1.

After suitable preparation he was operated on September 29, 1950, when a left lower pulmonary lobectomy and a segmental resection of the lingula were accomplished. The postoperative course was uneventful and he was discharged from the hospital, ambulant, on October 13.

He was next hospitalized on July 12, 1951, at which time he stated that since his operation there had been a marked decrease in the amount of sputum but that he still brought up approximately one cup daily. His condition was otherwise good. Physical examination was essentially negative with the exception of the scar on his left chest, which was a residual of the previous thoracotomy, and some coarse rhonchi heard over the right lower lobe. The physical findings in the right base were felt to be consistent with residual bronchiectasis. A preliminary roentgenogram of the chest showed residuals of the surgical procedure in the left thorax. Roentgenograms of the sinuses showed evidence of pansinusitis. Another bronchogram, made on July 16, 1951, again showed cylindric and saccular bronchiectasis of the right lower lobe and cylindric bronchiectasis of the right middle lobe (Figure 2). Otolaryngologic consultation was obtained, and on August 2, 1951, a submucous resection was performed and bilateral antral windows were made. Following convalescence from the sinus surgery his vital capacity was estimated to be about 73.5 per cent. He was observed carefully for functional impairment, and a work test of stair climbing showed him to be apparently normal in pulmonary reserve.

Preoperative preparation was again instituted and on September 6, 1951, a right

2a

2b

3

FIGURE 2. Bronchogram following left lower lobectomy and lingulectomy. The left thorax shows the residuals of the thoracotomy. The dilated bronchi on the right are well shown. FIGURE 3. The surgical specimen of right lower and middle lobes indicating the extensive involvement of the bronchi. FIGURE 4. The final, postoperative appearance of the bronchi on bronchography. The small area of residual bronchiectasis on the left is not demonstrable.

4

thoracotomy was performed and the right lower and middle pulmonary lobes were amputated. Convalescence from the operation was uneventful and he was discharged on September 17, 1951, ambulant and without complaints. He was recalled for examination in November 1951 but was unable to come at this time because he was farming and could not neglect his work.

He was re-examined in February 1952. At this time it was found that he had minimal cough and raised no more than a tablespoonful of sputum in the mornings. He felt greatly benefited by his operations and had regained much of his strength. Although he thought he became slightly dyspneic on exertion, he had purchased an acreage on which he was busy raising hogs and chickens.

Physical examination showed normal findings except for the thoracotomy scars on the chest. The blood pressure was 100/68 and the pulse rate was 68. The blood study was normal—red blood cells 4,300,000, white blood cells 7,100 and sedimentation rate 23 mm. per hour. A bronchogram showed the bronchi to be somewhat separated due to the hyperexpansion of the remaining lobes. They were normal in appearance, however, except for one (Figure 3). In the lower portion of the left upper lobe a slightly dilated bronchus was discovered. It was felt that this probably explained the small amount of sputum still being raised. The involvement was not considered extensive enough to be distressing, and the patient was discharged from any further observation.

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Clinical Experience with Tryptar in the Treatment of Infected Wounds

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TRYPTAR® *offers the surgeon another biologic approach to the therapy of infections. It is not a substitute for surgical therapy, but is a valuable adjunct. Illustrative cases are presented.*

J. M. MILLER

B. H. WHITE

PERRIN H. LONG

TRYPTAR, pure sterile crystalline trypsin, has been reported to be remarkably effective in the debridement of infected necrotic wounds[1] and in the treatment of fibrinopurulent empyema.[2] The enzyme is derived from mammalian pancreatic glands, is stable indefinitely in dry form at room temperature and is active over a *p*H range of 5 to 8, exhibiting its greatest activity at a *p*H of 7. The products of digestion are small polypeptides and some amino acids. When the powder is diluted in the accompanying vial of Sorensen's phosphate buffer solution, tryptar solution loses approximately 40 to 50 per cent of its proteolytic activity in three hours. The solution, therefore, must be freshly prepared each time before use.

Since tryptar is effective over a *p*H range of 5 to 8, it is advisable when using the powder either to determine the *p*H of the wound with nitrazine paper before treatment is started, or previously to irrigate the infected area with Sorensen's phosphate buffer solution for several minutes in order to assure a proper *p*H for maximal tryptic activity.

Tryptar can be applied to the area under treatment in a number of ways depending on the anatomic location of the lesion and the ingenuity of the surgeon. The powder may be

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TABLE 1

RESULTS OF TREATMENT WITH TRYPTAR IN 19 CASES

CONDITION	RESPONSE	
	Excellent	*Good*
Abscess in pilonidal cyst	3	
Abscess in soft tissues	5	
Carbuncle of neck	2	
Infected burn		1
Infected decubitus ulcer	1	1
Infected ulcer in diabetes mellitus		1
Perirectal abscess	5	
TOTAL CASES	16	3

sprayed on the wound with a DeVilbiss Powder Blower No. 119 or may be sprinkled on the wound directly from the vial. The solution can be applied as a wet dressing, by irrigation or by instillation. Most of the patients reported in this paper have been treated by direct application of an ointment to the affected area, a method of application of the drug not reported previously. The use of an ointment prevents loss of enzyme on a superficial wound, such as mechanical washing away of the powder by the serum and evaporation of the solution. Tryptar, 250,000 ARMOUR UNITS, dissolved in 20 cc. of Sorensen's phosphate buffer solution, was suspended in 50 cc. of LUBAFAX®, a water-soluble base. When stored in a refrigerator, tryptar in lubafax is stable for two days, as shown by spreading the ointment on roentgen film and noting the digestion of the gelatin thereon. Development of the film in the usual manner causes a precipitate of silver around the area of digestion. Trypsin digestion is shown as a clear spot on the film.

Nineteen patients with infections of varied types (Table 1) have been treated with tryptar in association with indicated surgery. It must be emphasized that tryptar is not a replacement for but an adjunct to surgical treatment when the latter is required. The presence of pus or necrotic material in closed spaces calls for incision and provision of a means for drainage. The instances following are illustrative of the manner in which tryptar has been used in combination with surgery.

Case Reports

Case 1—A 58 year old Negro was admitted to the Veterans Administration Hospital on April 11, 1951, with a carbuncle on the posterior portion of the cervical area of about 10 days' duration. The carbuncle measured approximately 8 cm. in diameter. Aqueous crystalline procaine penicillin G, 300,000 units, was given intramuscularly twice a day from April 11 through May 10. On April 13 the carbuncle was excised and a NYLON® pack was inserted into the wound. Cultures of the pus contained beta hemolytic streptococci and *Staphylococcus aureus*. Tryptar*, 15,000 Armour units, in lubafax, was applied to the wound once daily starting April 14 and continuing for 15 days through April 29. The wound became clean and showed healthy granulation tissue. A secondary closure was done on April 30. A minimal separation of a portion of the wound occurred, and healing was completed by secondary intention. The patient was discharged on May 15.

Case 2—A 35 year old white man was admitted to the Veterans Administration Hospital on April 24, 1951, with a large decubitus ulcer over the tuberosity of the left ischium, secondary to a paraplegia sustained as the result of an injury in January 1948. The patient had had many decubitus ulcers previously. A mechanical debridement was done on April 30. Starting on May 4 and continuing for nine days, through May 13, the wound (Figure 1) was treated with 25,000 Armour units of tryptar in 5 cc. of lubafax twice daily. SULFASUXIDINE®, 1 gm., was given orally every six hours from May 9 through May 15. AUREOMYCIN®, 0.25 gm., was given orally every six hours from May 9 through May 29. The wound became clean and showed healthy granulation tissue. On May 14 the scarred area about the wound and superior ramus, the tuberosity and the inferior ramus of the ischium were excised. The wound was completely closed with provision for lateral air vent suction catheter drainage, the catheter being removed on May 19. Although osteomyelitis was reported to be present in the removed bone, the wound healed uneventfully and the patient was discharged on May 29 (Figure 2).

*The Tryptar was supplied by The Armour Laboratories.

FIGURE 1. Decubitus ulcer, May 3, 1951, three days after debridement and one day before treatment with tryptar.

FIGURE 2. Healed wound on May 29, 1951.

Case 3—A 65 year old Negro was admitted to the Veterans Administration Hospital on June 26, 1951, with a carbuncle of the neck of 12 days' duration. A red, tender mass about 6 cm. in diameter was present on the posterior surface of the cervical region. The carbuncle was excised on June 27 and the wound was packed with nylon. *Staph. aureus* was cultured from the pus. Aqueous crystalline procaine penicillin, 100,000 units, was given intramuscularly twice a day from June 26 through July 31. Tryptar, 25,000 Armour units, in lubafax, was applied to the wound once daily from June 28 through July 12. On the following day, July 13, secondary closure was done since the wound was considered ready. A separation of a portion of the wound occurred and final healing was by secondary intention. The patient was discharged July 31.

Case 4—A 23 year old white man was admitted to the Veterans Administration Hospital on August 6, 1951, with an infected pilonidal cyst of one week's duration. Intermittent infection had been present for two years. An abscess about 7 cm. in diameter was noted in the sacrococcygeal area (Figure 3). An incision and means of drainage were provided on the day of admission. About 50 cc. of foul-smelling pus was released. *Streptococcus anaerobius* was found on culture. Aqueous crystalline procaine penicillin G, 100,000 units, was given intramuscularly every six hours from August 6 through September 7. Tryptar, 25,000 Armour units, in lubafax, was applied to the infected area daily from August 7 through August 20, when the involved area was considered ready for excision and closure (Figure 4). Operation was done on August 21 with provision of air vent suction drainage (Figure 5). Tryptar, 62,500 Armour units, dissolved in 5 cc. of Sorensen's phosphate buffer solution, was instilled into one of the catheters every six hours. The catheters were clamped for the next four hours and then suction was applied for two hours until the time for the next instillation. This treatment was given from August 22 through August 31 when the catheters were

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FIGURE 3. Abscess due to *Streptococcus anaerobius* in a pilonidal cyst on admission, August 6, 1951.

FIGURE 4. Wound on August 20, 1951, immediately after 13 days of tryptar treatment and one day before excision and closure.

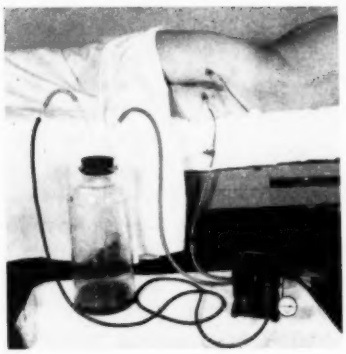

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FIGURE 5. Technic for providing air vent suction to closed wound.

FIGURE 6. Wound at time of discharge from hospital on September 7, 1951, one month and one day from date of admission.

6

removed. The main wound was healed on September 1 and the small wounds, through which the catheters were inserted, were healed on September 4 (Figure 6).

Case 5—A 33 year old Negro was admitted to the Veterans Administration Hospital on August 20, 1951, with an infection of the right ischiorectal fossa of four days' duration. Aureomycin, 0.5 gm., was given orally every four hours from August 20 through August 31, when the dose was changed to 0.25 gm. every six hours and continued until September 7. Incision and provision for drainage were done on August 21 at which time 30 cc. of pus was released from the wound. Culture of the pus showed an *Aerobacter aerogenes* and a microaerophilic gamma *Streptococcus*. Tryptar, 150,000 Armour units, in lubafax, was placed in the wound once daily from August 22 through September 5. The wound filled in rapidly with healthy granulation tissue and was completely healed except for a minimal lack of epithelium when the patient was discharged on September 7.

Case 6—A 23 year old white man was admitted to the Veterans Administration Hospital on August 21, 1951, with an abscess in a pilonidal cyst of five days' duration. The patient had had a pilonidal cyst for three years with repeated episodes of infection. A red, tender, fluctuant swelling about 5 cm. in diameter was present over the sacrococcygeal

area. Incision and drainage of about 25 cc. of malodorous pus were done on the day of admission. A microaerophilic gamma *Streptococcus* was cultured from the pus. Aureomycin, 0.5 gm., was given orally every six hours from August 21 through August 27. Aqueous crystalline procaine penicillin G, 100,000 units, was administered intramuscularly every six hours from September 3 through September 10. Streptomycin, 0.5 gm., was given intramuscularly twice a day from September 6 through September 7.

Tryptar, in an ointment, was placed in the wound once daily from August 22 through August 30. The wound became clean, with healthy granulation tissue. On August 30 the pilonidal cyst was excised and the wound closed primarily. Despite advice, the patient insisted on getting out of bed and caused a small separation in the lower portion of the wound. Healing was otherwise uncomplicated and the wound was closed on September 14 when the patient was discharged.

Comment

Tryptar, as used on 19 patients with infection, has proved a valuable aid in treatment. The enzyme cannot be considered a substitute for careful surgical therapy, and when the drug is used the surgeon must endeavor to arrange the local wound environment, if possible, to permit maximal action. Since the action of tryptar is optimal at or near body temperature, it may be advisable to apply external heat when the enzyme is used in wet dressings.

When tryptar was applied topically, a mild burning sensation locally was noted by some of the patients; injury to normal tissue was not observed. Although trypsin has been considered antigenic, allergic responses to tryptar were not observed. The histamine-like effect, described by Reiser, Roettig and Curtis[2] when tryptar was given intrapleurally or by hypodermic infiltration, has not been noted in our patients since the enzyme was not injected into a closed space. The patients of Reiser, et al.[2] were protected against this effect by the intravenous or oral administration of BENADRYL®. The action of tryptar is enhanced if free drainage of the infection is provided. Sinuses and fistulas leading to loculated cavities must be opened, for attempts to inject the enzyme into the loculations will not give optimal results.

Tryptar changes thick, viscid exudate into a thin, fluid material, and if adequate provision for drainage has been made the pus can easily be removed from the wound. The removal of thick, purulent exudate permits not only better phagocytosis but also better penetration of the recesses of the wound by chemotherapeutic or antibiotic agents given orally or systemically.

Tryptar in the concentrations used does not injure living cells and does not produce ecchymoses, hematomas or petechiae after topical application. Tryptar injected through catheters in Case 4 did not cause hemorrhage and did not interfere with healing of the wound.

The catheters provide a method of putting the active agent where it is needed most. A dead space in which clotted blood and serum accumulate is usually present in such instances of pilonidal cysts in spite of meticulous surgery, and these accumulations are good mediums for bacterial growth. Tryptar will liquefy this thick fluid, thus permitting easy aspiration by air vent suction and obliteration of the dead space. The sulfonamides or antibiotics may be given orally or systemically at the same time that tryptar is administered topically. If chemotherapy or antibiotic therapy is indicated, adequate doses of the chosen agent should be administered concomitantly with tryptar.

Tryptar will not heal the ulcers associated with peripheral vascular disease if the blood supply to the part is not adequate. The control of infection by tryptar may permit healing if the blood supply is adequate.

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Medical Illustration

The Biological Photographic Association

In September 1931 a small group of biological photographers met at Yale University to organize an association dedicated to "further the study and application of photography in relation to the biological sciences, and to improve its technic." Since that time, the Association has continued to grow until it is now a national organization with chapters in several cities.

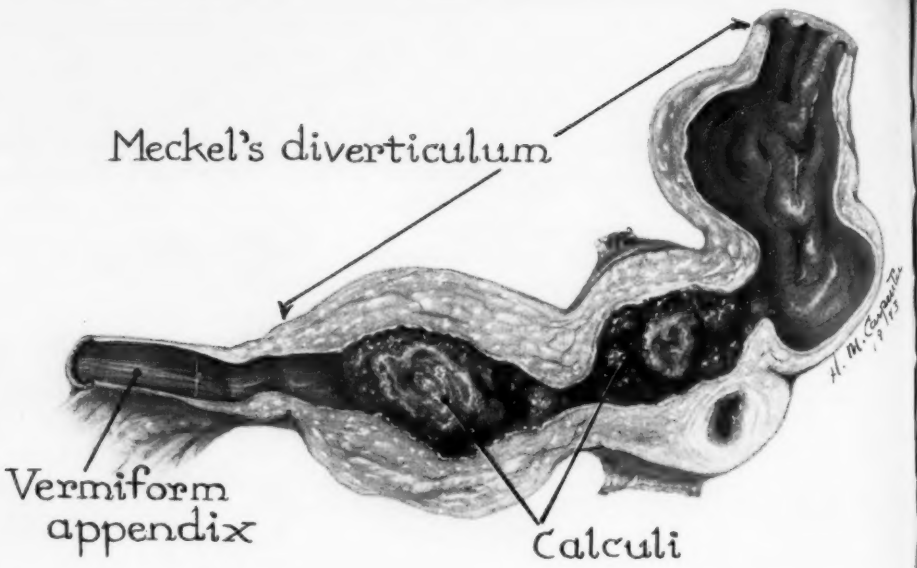
An important phase of the biological photographer's work is to help the physician who wishes to present a paper at a meeting, prepare an article or book for publication, assemble a scientific exhibit, or have a complete study for his own patient files, to obtain the best possible photographic material for reference or reproduction. Other photographic functions include the preparation of motion pictures of surgical procedures, pictorial material for hospital and clinic public relations efforts, and associated projects.

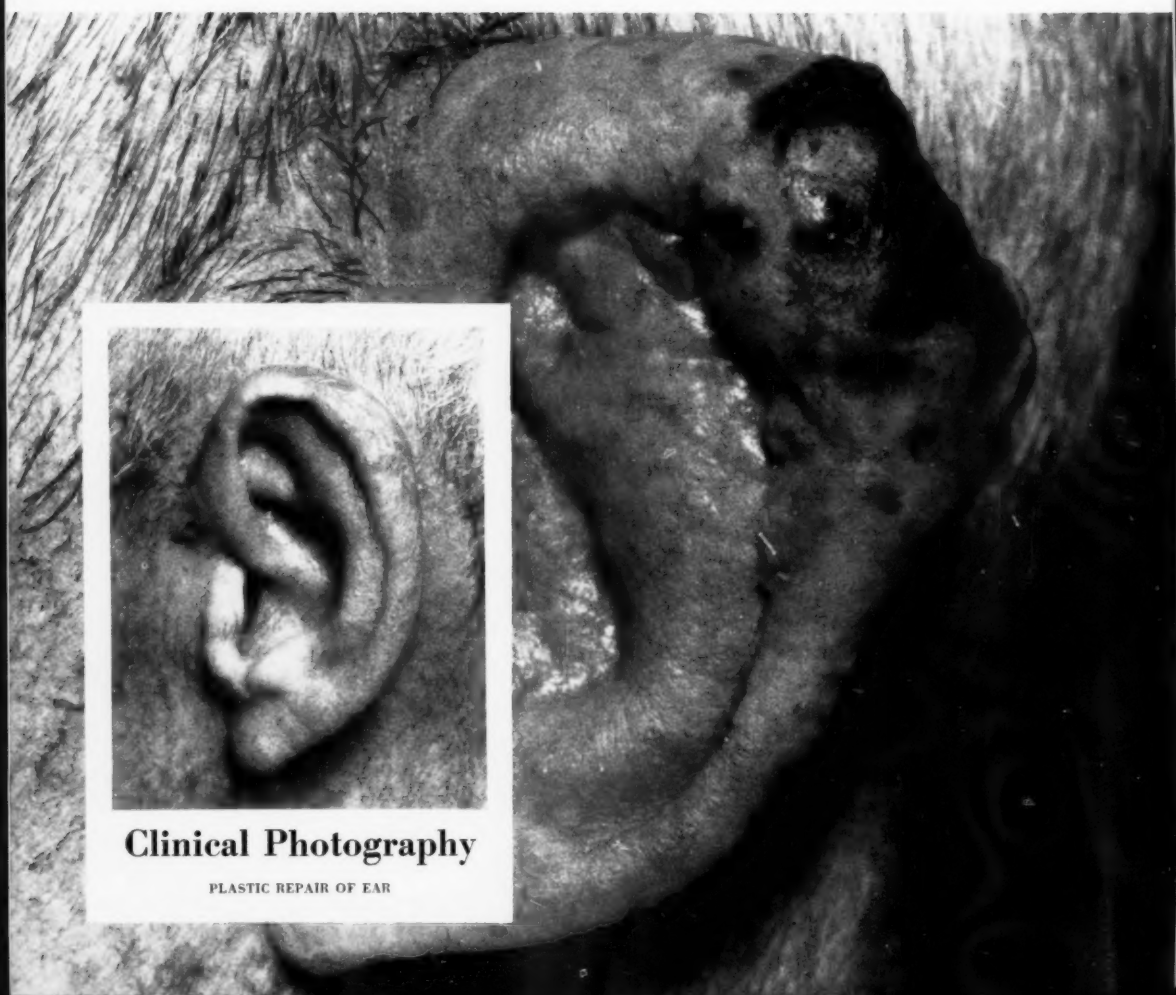
In this exhibit, displayed at the last annual session of the American Medical Association, are presented selected examples of various types of photographic studies and the purposes they serve.

Acknowledgment is made to the Department of Medical Illustration, John E. Withee, director, the Hitchcock Foundation, Hanover, New Hampshire and to Lloyd E. Varden, former national secretary and now editor of the Journal of the Biological Photographic Association. *The color plates have been reproduced through the courtesy of* Medical Radiography and Photography, *published by Eastman Kodak Company.*

Graphic Illustration

MECKEL'S DIVERTICULUM

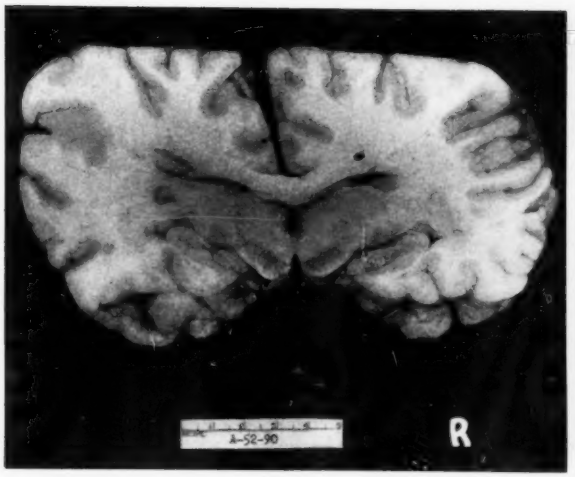




Clinical Photography

PLASTIC REPAIR OF EAR

Photography of Gross Specimens



TUBERCULOMAS OF BRAIN

LEFT LUNG

Radiographic Copying

BRAIN TUMOR

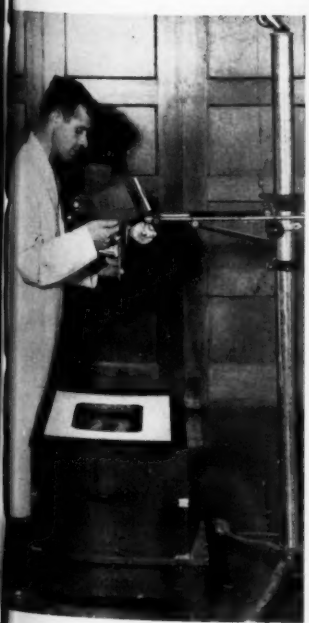
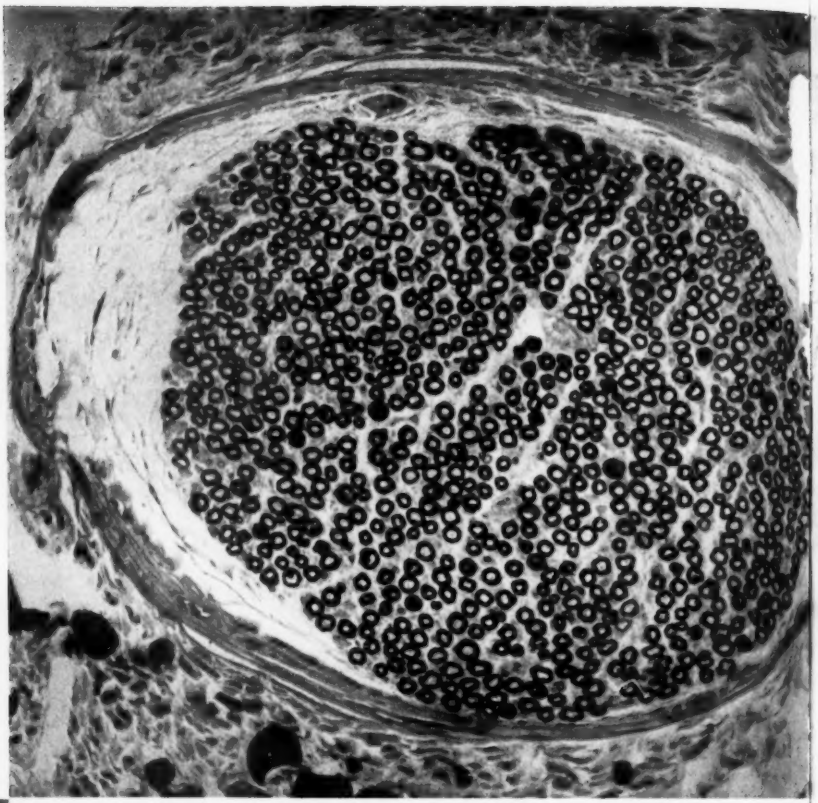


Photo-micrography



CROSS SECTION OF
HUMAN NERVE

BAUSCH & LOMB TYPE R
HORIZONTAL CAMERA

Medical Motion Pictures

CAMERA STAND FOR OPERATING ROOMS

TRICHINA WORM
IN MUSCLE

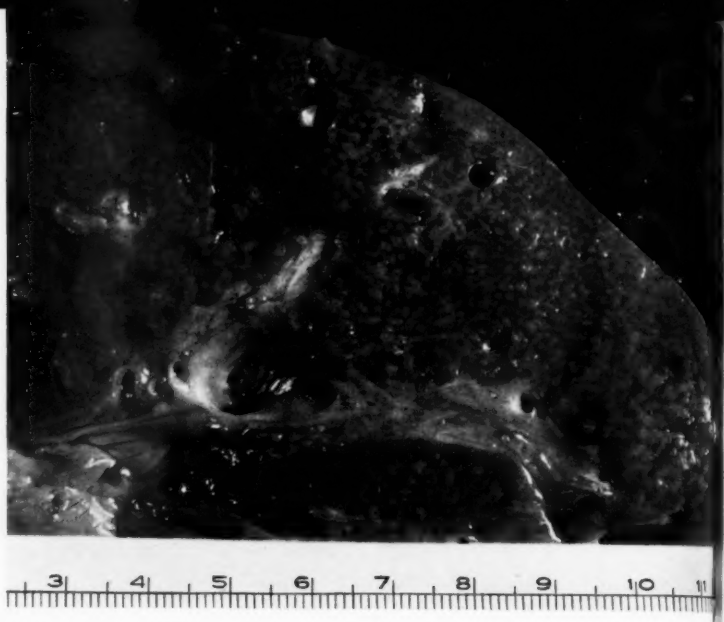
Hospital Public Relations

AIR AMBULANCE SERVICE

POLIO PATIENT WITH THERAPIST

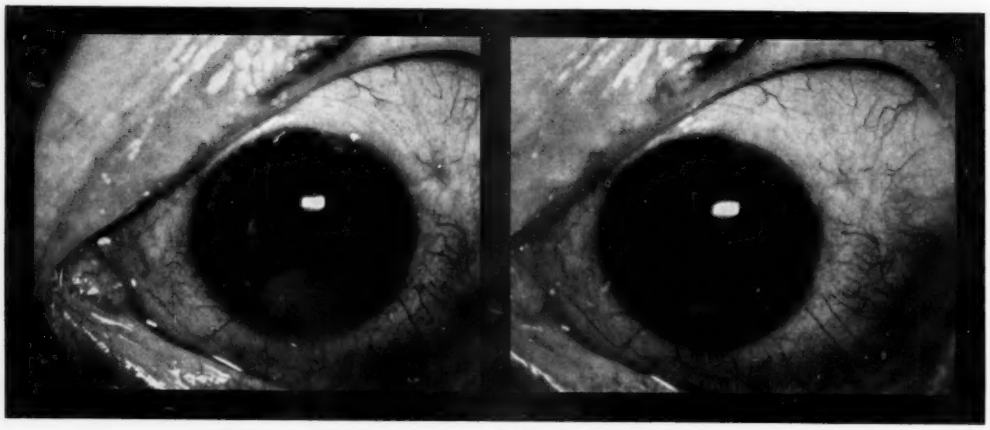
Color Photography

CARDIAC CIRRHOSIS OF LIVER *(right)*—Photograph by Mrs. M. W. Miles, Youngstown Hospital Association, Youngstown, Ohio.



LEUKOPLAKIA AND CARCINOMA OF BUCCAL MUCOSA *(below)*—Photograph by Department of Photography, Pathology Laboratories, Rochester General Hospital, Rochester, New York.

CROSS SECTION ... VERTEBRAL COLU... WITH NUCLEUS P... POSUS EXTRUDI... *(above)*—Phot... graph by Miss ... E. Kerr and Miss ... A. White, Roch... ter General H... pital, Rochest... New York.



STEREOSCOPIC PHOTOGRAPHS OF SECONDARY CATARACT WITH SOFT LENS MATERIAL IN ANTERIOR CHAMBER—Photograph by E. Rosenthal, M.D., Hartford, Connecticut.

GENERAL PRACTICE *Review*

This department offers the latest, proved methods for the treatment and management of commonly encountered conditions based on the extensive experience of the physicians who prepare these summaries for POSTGRADUATE MEDICINE.

Hepatic Cirrhosis and Its Complications

CLARENCE W. LEGERTON, JR.*

Duke University School of Medicine, Durham, North Carolina

THE term "cirrhosis," from the Greek *kirrhos*, meaning orange-colored or tawny, has outlived its usefulness. The color of the cirrhotic liver is of little importance. Rather it is the presence of fibrous tissue in such a liver that accounts for the morbidity and mortality of this process.

CLARENCE W. LEGERTON, JR.

The normal liver reacts to injury in at least two nonspecific ways—by fibrosis or by regeneration. These processes are in no way a characteristic response to a specific cause, but rather a normal reaction to numerous forms of hepatic injury. Thus cirrhosis, which is more aptly termed diffuse hepatic fibrosis, should not be regarded as a clinical entity but rather as the end result of repeated or prolonged injury to the liver.

Pathogenesis

Diffuse hepatic fibrosis may result from a variety of insults to the liver—nutritional, toxic, circulatory or infectious. However, the word cirrhosis as used clinically implies the presence of portal cirrhosis, and I shall discuss only this form.

The primary liver injury is a prolonged nutritional deficiency, frequently combined with alcoholism, producing fatty infiltration of the liver which in turn eventuates in diffuse hepatic fibrosis. The diet of patients with cirrhosis is frequently deficient in protein and in factors which prevent the accumulation of fat in the liver. These substances are termed "lipotropic" and include the essential amino acid methionine and choline.

Alcohol certainly plays a contributing role in this process. Whether its effect is primary through a direct toxic action on the liver cells or secondary by its effect on decreasing the food intake is still unsettled.

Clinical Features

The symptomatology of hepatic failure, which begins late in the disease, can be classified into three general syndromes: (1) parenchymal failure, (2) excretory failure and (3) portal obstruction.

Parenchymal failure—It has been estimated

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Diagrammatic Representation of the Channels of Collateral Circulation which may develop in Hepatic Cirrhosis

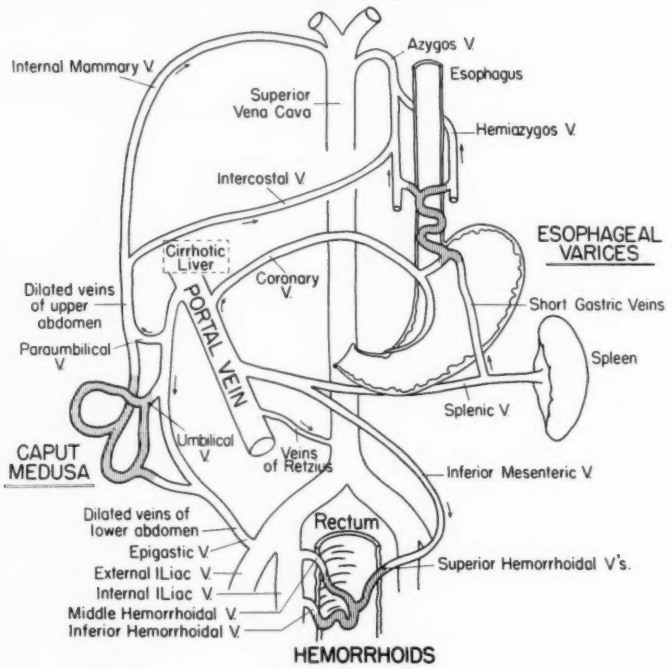

FIGURE 1

that 80 per cent of the polygonal cells must be damaged before symptoms develop. Anorexia, nausea, vomiting, postprandial distention, gaseous eructation, bowel irregularities and weight loss are frequent initial complaints. It is well to remember that pain is a common early symptom, being found to some degree in roughly 50 per cent of the cases. This pain is usually vaguely described and poorly localized. Typically it is a dull epigastric or right upper quadrant ache, aggravated by exercise and food, and probably related to tissue and circulatory changes in the organ rather than to capsular tension. Deficient prothrombin production may result in bleeding phenomena such as epistaxis, purpura or bleeding gums. Altered estrogen metabolism is thought to be causative in the production of the interesting phenomena of spider angiomas, palmar erythema and alteration of secondary sexual characteristics. The typical vascular spider is seldom found below the umbilicus. Erythema is usually found on the thenar and hypothenar eminences of the palms, and rarely on the finger pads or soles of the feet. In men, impotence and loss of libido are common; true gynecomastia, female pubic hair pattern and testicular atrophy are much less frequent. A peculiar sweet "musty" odor of the breath, termed fetor hepaticus or liver breath, may become evident as the disease progresses. A low grade fever may also be present and, like the liver breath, is thought to be related to hepatocellular necrosis. The neurologic manifestations of cirrhosis are usually those of peripheral neuritis, on the basis of nutritional deficiency and alcoholism. Euphoria, mania, mental confusion and toxic delirium occur late in the disease. Coma usually appears terminally.

Excretory failure—Failure of the liver to excrete bile is associated with a rise in the levels of alkaline phosphatase, cholesterol, bile salts and bilirubin in the blood. The first of

these produces no symptoms, the second only in rare instances gives rise to xanthomatous plaques, and the third is said to account for pruritus which is occasionally present. The retention of bilirubin results in jaundice, which is the symptom par excellence of excretory failure.

Portal obstruction—The demonstration of a collateral circulation between the portal and the systemic venous system is definite evidence of portal obstruction. These collateral vessels may be found at three sites: (1) the junction of the esophagus and stomach, (2) the junction of the rectum and anal canal and (3) the umbilicus (Figure 1). These distended veins are most commonly found in the esophagus and are usually demonstrable by x-ray (50 to 60 per cent of cases). The presence of hemorrhoids is of little diagnostic significance and a caput medusae is rarely seen.

Splenomegaly, in association with chronic hepatic disease, is dependent on two factors. First and most important is the mechanical factor of portal hypertension. Second is the toxic factor, derived from the degenerating liver cells and producing hyperplasia of reticulum cells. A palpably enlarged spleen is found in 60 to 80 per cent of the cases of cirrhosis.

Ascites is the most frequent and characteristic sign of hepatic cirrhosis, occurring in at least 80 per cent of the cases. Its occurrence is dependent not only on portal hypertension but also on reduced osmotic pressure of the plasma secondary to hypoproteinemia, the altered state of capillary permeability and the failure of the body to excrete salt and water adequately in the face of liver damage.

Ankle edema may precede ascites and, if so, the plasma albumin level is always decreased, usually below 3 gm. per cent. A moderate rise in serum globulin may be found at this time, since it is formed from sources other than the liver, while albumin is not.

Laboratory Tests

In evaluating cases of suspected hepatic cirrhosis, sensitive tests of liver function should be employed initially. These should include (1) serum bilirubin, (2) the cephalin-cholesterol flocculation test, (3) the combined thymol turbidity and flocculation test and (4) in the absence of jaundice, the 45 minute, 5 mg. per kilogram, photoelectric BROMSULPHALEIN® test.

If these tests are positive, one should proceed to less sensitive tests in order to evaluate the degree of hepatic damage present. Tests in this group comprise (1) the serum albumin level, (2) the blood prothrombin time and (3) the blood cholesterol determination (both total and esters).

Serial determinations of these tests are of importance not only in diagnosis but also in following the results of treatment, evaluating the operative risk and determining the prognosis in the individual case.

Diagnosis

The ease in diagnosing cirrhosis depends on the stage to which liver insufficiency has progressed. However, if one is to forestall liver failure the diagnosis must be established with certainty before irreversible hepatocellular damage has occurred. In a patient with chronic dietary deficiency and alcoholism, in whom weight loss and anorexia are accompanied by mild jaundice with enlargement of the liver and spleen, the diagnosis of cirrhosis is easily established. The finding of liver palms, spider angiomas or liver breath is further evidence, and the demonstration of esophageal varices confirms the diagnosis.

The presence or absence of cirrhosis can be demonstrated accurately by liver biopsy. Moreover, the relative degree of inflammatory reaction, cellular necrosis, fatty infiltration and fibrosis can be determined. Fatty vacuolization is an indication for lipotropic agents, while marked fibrosis points to the futility of such therapy. Likewise the liver biopsy can exclude the diagnosis of cirrhosis and, in some cases, simultaneously bring to light some other disease such as carcinoma or hemochromatosis. Serial biopsies may be used to determine the results of treatment.

Management

General—The patient with severe and active hepatic disease should be confined to

bed, as it has been shown that liver blood flow is maximal in the recumbent position. The necessity for adequate nursing care is obvious, especially in the mentally confused patient. Intercurrent infections are to be guarded against, and elective surgical procedures should be postponed.

Oral and parenteral feeding—Food is the medicine of choice in the treatment of cirrhosis. Every effort should be made to insure an adequate and varied dietary intake. It should be remembered that food must be not only prescribed but eaten as well. Anorexia, which is commonly present, may respond to parenteral vitamin B complex, with or without crude liver extract. The use of small doses of insulin before meals is of questionable value. In general, one should plan for an intake of at least 125 gm. of protein and 350 gm. of carbohydrate daily. Caloric intake can be increased by carbohydrates of all types, since they are well tolerated by the sick liver. Between-meal use of sweetened fruit juices and hard candy is an old standby of proved value. Strict limitation of fat results only in an unpalatable diet, and sufficient fat to preserve taste and appetite appeal—in the form of cream, butter, cheese, milk and milk products—is not injurious in the presence of an adequate protein intake. This will usually be in the neighborhood of 100 gm. daily. One must attempt to adjust the patient's dietary intake to the maximal level which can be tolerated by his disturbed gastrointestinal tract, since overloading with its resultant nausea, vomiting or diarrhea may worsen the patient's already precarious position.

Intragastric feedings, preferably through thin-walled plastic tubes which minimize trauma to varices, should be given only to those patients who make no effort to eat but whose gastrointestinal tracts could tolerate larger quantities of food than patients will ingest. Such feedings offer the advantage of ignoring matters of taste, both as to individual foods and to the rather unpalatable low salt diet.

A patient so ill as to be unable to take anything by mouth must be maintained on intravenous feedings. The amount needed daily is 3500 to 4000 cc., mainly 10 per cent glucose solutions to which have been added B complex vitamins, ascorbic acid and vitamin K. Protein hydrolysate solutions may be utilized by the diseased liver, and the addition of 1 gm. of potassium chloride daily to the glucose infusion will protect against severe potassium deficiency. Unless the patient is accumulating fluid, 5 per cent glucose in normal saline will provide necessary electrolytes.

A low sodium diet is indicated only when marked ascites or edema, or both, occur. Paracenteses, which are indicated initially to relieve respiratory, cardiac or digestive distress, are usually made unnecessary by this type of diet. Mercurial diuretics may hasten the removal of fluid, but the danger of hyponatremia with its attendant impaired renal function, vomiting and collapse must be continually kept in mind. The use of ammonium chloride may potentiate the mercurial effect, but routine use is inadvisable because of occasional gastric irritation. Cation exchange resins, which prevent the absorption of sodium from the intestines, are gritty and unpalatable. Their use may further depress the appetite, and frequent determinations of sodium and potassium are necessary with this therapy.

Supplements—Vitamins must be supplied by the most feasible route in the individual case. Oral multivitamin capsules, with vitamin B complex in the form of brewer's yeast or liver extract, should be given. In the rare case, the patient will require specially prepared liver extract given intravenously. Supplementary administration of individual B vitamins is indicated only in the presence of beriberi, pellagra, ariboflavinosis or marked malnutrition. Although the sick liver utilizes vitamin K poorly, the daily oral or parenteral administration of a water-soluble preparation is advisable. If the prothrombin time does not respond, transfusions of fresh whole blood are indicated where bleeding is a problem. Vitamins A, D and E are usually adequately supplied in the multivitamin preparations.

Other therapeutic agents—Lipotropic agents such as methionine and choline are unnecessary in the face of an adequate and nutritious diet. In a patient unable to eat an

THERAPEUTIC AGENTS USED IN MANAGEMENT OF CIRRHOSIS

Adequate and varied dietary intake
Bed rest (in active stage)
Supplements

If adequate diet cannot be ingested:

- Brewer's yeast powder, 30 to 45 gm. daily in water, milk or eggnog
- Multivitamin capsules
- Choline chloride, 2 to 5 gm. daily
- Combination of latter two—METHISCOL®, 3 capsules three times daily
- Crude liver extract, 1 to 2 cc. intramuscularly daily
- ESSENAMINE®, protein concentrate, 1 to 2 tablespoons three to five times daily
- Liver extract for intravenous use—INTRAHEPTOL®

In the presence of ascites or edema:

- Low sodium diet
- Salt substitutes—NEOCURTASAL® or CO-SALT®
- LONALAC®, a low sodium milk product
- Enteric-coated ammonium chloride, 2 gm. orally three times daily
- Mercurial diuretics—THIOMERIN®, MERCUHYDRIN®—1 to 2 cc. intramuscularly daily for three to four days, then less frequently
- Concentrated salt-poor human serum albumin, given intravenously, 75 gm. or 300 cc. of 25 per cent solution daily for five days, then 50 to 75 gm. once or twice weekly thereafter

In the presence of bleeding tendencies:

- Vitamin K, SYNKAYVITE® or HYKINONE®, 5 mg. twice daily
- GELFOAM® thrombin solutions, orally
- Whole blood transfusions
- Esophageal balloon (Blakemore)*
- Surgical procedures to relieve bleeding varices

Antibiotics

- Penicillin, 600,000 units daily
- Aureomycin, 0.25 gm. four times a day

Of doubtful value

- ACTH and cortisone
- Cation exchange resins fortified with potassium (CARBO-RESIN®)
- SORLATE® (sorbitan mono-oleate), 1.5 gm. three times daily (wetting agent)

*Davol Rubber Company, Providence, Rhode Island.

ordinary diet, especially if the liver is large and biopsy has shown the presence of fat, administration of these agents may prove beneficial.

Albumin, in its salt-poor form, is occasionally effective in controlling ascites, but because it diffuses readily into the ascitic fluid it is frequently of little value. Its inconstant therapeutic results and occasional serious side effect—increased blood volume, leading to massive hematemesis or pulmonary edema—make it less satisfactory in the control of ascites than restriction of salt. Likewise it is inferior to the more readily metabolized protein hydrolysates as a source of protein nutrients.

The protein-sparing effect of testosterone is more economically achieved by simply increasing the protein and caloric intake.

Whole blood transfusions are useful in the treatment of anemia, shock, coma and bleeding tendencies. Blood loss must be combated rapidly and vigorously, since the diminished hepatic blood flow incident to hemorrhage further damages the already impaired liver.

Oxygen by tent or catheter should be reserved for the patient in coma or showing signs of impending coma.

Antibiotics are indicated when hepatic damage is being aggravated by intercurrent infections, especially if fever is present. AUREOMYCIN® and terramycin are indicated when the infection is known to respond only to these agents. Otherwise, the commonly seen gastrointestinal disorders, especially diarrheas, following these drugs make their use unwise. Penicillin is the drug of choice in treating suspected infection, especially since hepatic disease predisposes the patient to pneumococcal infections. Aureomycin may be given a trial in patients with hepatic coma.

ACTH and cortisone have been used for too short a time and in too few patients for adequate evaluation. Often a temporary improvement has been noted, manifested by increased appetite, a sense of well-being and a gain in weight. These effects, however, may be counterbalanced by fluid retention in the form of ascites or increasing edema. Therefore these agents are not clearly indicated in the treatment of severe hepatic disease.

Sedatives exert prolonged and occasionally serious effects in hepatic disease, especially in the terminal stages. Opiates of all types are contraindicated. Barbiturates in small doses are tolerated better by the sick liver than is

generally thought. This is especially true of the long-acting group, as these are to a large extent excreted by the kidneys. When sedatives are necessary, paraldehyde and chloral hydrate are agents of choice.

No satisfactory curative treatment for bleeding esophageal varices is available. Use of vitamin K and locally applied blood-clotting agents is ineffective. Tamponade, by means of especially devised esophageal balloons, may be lifesaving, and such balloons should be available. Surgical procedures, such as injection of varices, resection of the vein-bearing area, and the various portal-systemic shunting operations have not been done long enough or on enough patients to be critically evaluated. In the hands of a specifically trained and skilled surgeon, the shunt procedures have shown beneficial results in selected cases. Marked ascites which does not clear on medical therapy, a serum albumin of less than 3 gm., or flocculation tests in the range of 3 to 4 plus are contraindications to such operations. Splenectomy alone is of questionable value, and if done in the face of portal hypertension it should be accompanied by a splenorenal anastomosis.

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Pregnancy and Labor in the Cardiac Patient

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The association of heart disease and pregnancy is of serious import to the patient. The immediate and remote prognosis is frequently uncertain, and the course of the cardiac patient who becomes pregnant must be guided by intelligently planned care of (1) the cardiac condition and (2) the pregnancy.

To approach this problem correctly it is necessary to revise completely the unfortunately prevalent ideas concerning the interrelationship between pregnancy and heart disease. The medical literature is replete with reports and discussions based on the theory that the pregnancy is the primary condition and the cardiac disease the complication. In the light of present knowledge the existing cardiac disease must be regarded as the primary condition and the pregnancy as the complication. Only in this way are the best results obtainable.

While pregnancy becomes less ominous to the cardiac patient with the adoption of this attitude, it still presents certain definite problems. Pregnancy places a mechanical burden on the heart because of the increase in the vascular bed, the blood flow and the blood volume. The increase in output amounts to at least 25 per cent by the fourth month of pregnancy and between 50 and 60 per cent at term. It is important, therefore, to consider the additional burden on the heart during pregnancy.

Cardiac Abnormalities Encountered

Murmurs—Functional cardiac murmurs occur frequently during pregnancy, and at least 6 to 10 per cent of women will have such functional murmurs at some time during the course of pregnancy. These murmurs are without significance, are not evidence of cardiac disease and may be completely disregarded.

Extrasystole—A second type of functional disturbance of the heart which is found with some frequency during pregnancy is the occurrence of extrasystoles. These are usually intermittent and occur with increasing frequency during the last trimester of pregnancy. They are of no significance without other evidence of cardiac disease and practically always disappear after labor.

Congenital heart disease—Congenital heart disease is uncommon, and of all patients with pathologic conditions of the heart less than 2 per cent have the congenital type. With careful evaluation and proper management the majority of patients with congenital heart disease can be carried successfully through pregnancy and labor. It must be emphasized that the various congenital lesions must be carefully evaluated, since pregnancy can be very deleterious in the presence of certain types, particularly patent ductus arteriosus or tetralogy of Fallot.

Rheumatic heart disease—Rheumatic heart disease, with involvement of the mitral valve by stenosis and/or insufficiency, is by far the most common type of heart disease encountered in pregnancy (85 per cent). A small percentage will show involvement of the aortic valve, either independently or in association with mitral involvement.

Cardosis—Lastly, some patients may show evidence of mild cardosis resulting from arteriosclerosis, hypertension, nephritis and hyperthyroidism. Coronary disease is unusual, although it occasionally has been reported.

Prognosis

When pregnancy faces the cardiac patient, the question of prognosis becomes all-important. It is of interest to note that many patients with definite rheumatic heart disease will go through repeated pregnancies with apparently no ill effects. It must be assumed that the cardiac disease in these patients is stationary rather than progressive. It must further be assumed that there was no myocardial damage since cardiac efficiency is not dependent on the type or extent of the valvular lesions. *A heart is as good as its myocardium.* The type and severity of the valvular lesion are secondary in attempting to establish prognosis; the clinical and laboratory evidence of the severity of the myocardial involvement must serve as the guide for management. A history of cardiac decompensation, reactivation of the acute rheumatic episode, evidence of cardiac enlargement, and the signs and symptoms of pulmonary congestion, together with electrocardiographic evidence of myocardial damage, coronary disease, heart block, intraventricular block, tachycardia and fibrillation, are all ominous and give a bad prognosis. These must be correlated with the patient's tolerance of physical activity in order to evaluate properly the course of pregnancy.

Index of Functional Capacity

The functional capacity of the heart is difficult to evaluate clinically. Exercise tests do not give the information necessary to determine what a heart will do under the strain of pregnancy and labor. At present our best index of functional capacity of the heart is the grouping of patients by the classification of the New York Heart Association. By this method cardiac capacity is evaluated by the patient's history, both present and past, and is all-important in classifying patients:

Class 1—Patients with cardiac disease and no limitation of physical activity. Ordinary physical activity does not cause discomfort. Patients in this class do not have symptoms of cardiac insufficiency, nor do they experience pain.

Class 2—Patients with cardiac disease and slight limitation of physical activity. They are comfortable at rest. If ordinary physical activity is undertaken, discomfort results in the form of fatigue, palpitation, cough, dyspnea or anginal pain.

Class 3—Patients with cardiac disease and marked limitation of physical activity. They are comfortable at rest. Discomfort in the form of undue fatigue, palpitation, cough, dyspnea or anginal pain is caused by less than ordinary activity.

Class 4—Patients with cardiac disease who are unable to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency are present even at rest. The discomfort is increased if any physical activity is undertaken.

The clinical course of the cardiac patient during the period subsequent to her last pregnancy frequently affords an excellent index of safety in regard to future pregnancies. However, the fact that a damaged heart will go through pregnancy and labor without symptoms and without any evidence of cardiac embarrassment or failure should not be taken as a criterion for subsequent pregnancies. This is particularly true in mitral disease of rheumatic origin, a condition which is notoriously progressive and which can, and frequently does, result in increasing myocardial damage during the months or years intervening between pregnancies.

Classes 1 and 2—Patients who fall into classes 1 and 2 obviously have good myocardial reserve. These patients may be permitted to go through pregnancy and labor, provided they are cooperative and will receive meticulous and continuous prenatal care and supervision during labor. The most important factor during pregnancy is adequate rest. Such patients must be given sufficient instructions as to what may or what may not be done. They should have at least 10 hours' rest each night, and must lie down for a short period after each meal. Light housework and walking on the level may be permitted. Stair climbing must be kept at a minimum. Prolonged shopping tours, heavy housework and other forms of physical strain must be avoided. The patient must not take any form of exercise, must spare herself as much as possible and must have as much rest as possible.

Such a proper restriction of physical activity and the ability to carry out enforced rest throughout the pregnancy is sometimes difficult. Here the social status plays a role. The cardiac patient of means can insure the maintenance of her cardiac compensation to a large extent by prolonged rest. The working woman who must continue her household duties and her care of the family is apt to decompensate much more frequently. It has been shown repeatedly that cardiac failure during pregnancy is twice as frequent among service patients as among a private clientele. In order that the morbidity and mortality rates of the two groups may be the same, service patients must have available the same opportunity for necessary rest during pregnancy, and particularly during the puerperium, as do the private patients. This means that another woman should live in the house with the pregnant woman to relieve her of much of the routine duties of the household and to insure her periods of rest.

The avoidance of infections, particularly of the upper respiratory tract, is important. It is difficult for the pregnant cardiac patient to isolate herself or to avoid such infections, particularly if there are small children in the family. It is important, then, that the cardiac patient pay special attention to upper respiratory infections, to avoid, if possible, all contacts and to go to bed immediately and for a prolonged period whenever she develops an upper respiratory infection.

The cardiac patient who is pregnant should be carefully examined every two weeks throughout pregnancy. She should be told that the most frequent early symptom of an impending decompensation is the development of the cough, which usually makes its appearance before the development of dyspnea or edema. The physician must be notified immediately whenever any of these signs develops. The patient must be put at absolute bed rest and the usual measures taken to

avoid decompensation. These precautions may sound excessive for patients who fall into class 1 or 2. However, it must be borne in mind that errors in classification are all too frequent and many patients are classified incorrectly and will suddenly develop serious decompensation.

Since heart disease is the next most frequent cause of maternal death following those due to infection, hemorrhage and toxemia, it must be obvious that many cardiac patients who become pregnant are not receiving sufficient care to avoid the dangers of decompensation during pregnancy, labor and puerperium.

Patients in classes 1 and 2 will, under ideal conditions, begin labor with cardiac reserve. It would be ideal, were it feasible, to hospitalize all these patients for 10 to 14 days prior to the onset of labor. The overwhelming majority in class 1, however, do not require such precautionary measures, but for those in group 2 they would be of real therapeutic value. As a substitute, increasing rest at home will serve almost as well during the later days of pregnancy. There is no purpose in digitalizing such patients during pregnancy or labor. Digitalis should be administered only when the signs of cardiac embarrassment actually develop.

During active labor the patient should be kept in a semirecumbent position. Pulse and respiration must be constantly observed. A pulse rate above 110 or respiration above 24, with or without cough or dyspnea, is the early sign of the development of cardiac embarrassment and calls for prompt use of large doses of digitalis, both orally and intravenously.

The maintenance of cardiac compensation during the first stage of labor can be aided by the adequate use of morphine, sedatives and various analgesics. The use of morphine still furnishes the best means of insuring rest during labor and of resting the damaged heart. Therefore, the liberal use of morphine is doubly indicated for the cardiac patient during the first stage of labor.

A definite amount of muscular effort is required to complete the second stage of labor spontaneously. It is generally agreed that the repeated effort of bearing down is too great a strain to place on a diseased heart. Hence the universal admonition that the second stage of labor be eliminated. In the abstract this would seem to be correct, since the amount of muscular work necessary for a spontaneous second stage is dependent on a combination of many factors, such as multiparity, size of the fetus, pelvic measurements and condition of the soft parts. It does not seem judicious to generalize too completely. Many cardiac patients go into labor early while the fetus is still small, and in many, labor is unusually short. These patients may be permitted to go into the second stage of labor and have the labor safely terminated by outlet forceps and episiotomy. When the second stage of labor does not progress rapidly and simply, or when it seems as though the second stage might be prolonged, or in those patients in whom the effort of bearing down cannot be avoided, it is much safer to terminate the labor by forceps extraction.

The ideal anesthesia for these patients is local infiltration or pudendal block. The general anesthetic of choice for the cardiac patient is ether, which is well tolerated and serves as a cardiac stimulant.

Sudden collapse in the third stage of labor can and does occur even in those patients who have shown no evidence of cardiac distress during pregnancy or labor. This is a small but very definite risk for the cardiac patient. The more or less sudden decrease in intra-abdominal pressure coupled with the lowering of the diaphragm and the abrupt change in the cardiac axis are all factors which can lead to sudden cardiac collapse. In order to avoid such catastrophies it is advisable to apply a tight abdominal binder immediately after the placenta is delivered or to place sand bags on the abdomen concurrently with the expulsion of the child. This latter method is in use in many institutions and seems to be more effectual than the abdominal binder.

The danger of cardiac failure continues to be a threat during the first 10 days of the puerperium. Occasionally, decompensation will occur between the fourth and seventh day

and may be associated with the onset of diuresis. All cardiac patients should be kept in the hospital and at rest for at least two weeks following delivery.

Upon discharge from the hospital the patient should be carefully instructed as to the necessity of continuing precautions and the maintenance of adequate rest after she has returned home. Many a cardiac patient experiences her first or a repeat episode of decompensation during the late puerperium. The resumption of household duties together with the added burdens imposed by the new baby and the resumption of a normal marital life frequently put an undue burden on the cardiac patient. It is necessary, therefore, to take added precautions during this period in order to avoid the occurrence of decompensation and cardiac failure after the patient has been discharged from the hospital.

Class 3—Patients in class 3 should not become pregnant. The hazards of pregnancy, labor and the puerperium impose too great a risk on these women, and pregnancy is therefore contraindicated. Obviously, pregnancy does occur in class 3 patients—either because of a sentimental desire to have a baby or because patients refuse to avail themselves of contraception. Many women will deliberately run the added risk because of their intense desire for offspring. The complete understanding of the risks involved, by both patient and family, and their complete cooperation are necessary for a safe outcome. The cooperation of the patient in following most completely the rules laid down for the care of the pregnant cardiac woman are absolutely necessary. Furthermore it is advisable that these patients spend one or two days of each week in bed to avoid strain.

Cardiac decompensation during pregnancy requires immediate hospitalization and digitalization, following which the signs and symptoms of decompensation frequently disappear promptly. Such a patient, even though she has completely re-established cardiac compensation, should be kept in the hospital for the remainder of her pregnancy. It is always tempting to release such a patient once compensation has been re-established. This is a mistake, since experience shows that the overwhelming majority of such patients will, if allowed to go home under any type of restriction, again decompensate.

Vaginal delivery is definitely safer for all cardiac patients and particularly for those who have recently been in failure or who are in failure at the time of delivery. Heart disease must never be an indication for cesarean section. It is a definite contraindication, since the cardiac patient does not tolerate major surgery well. Obviously there are times when an obstetric indication for cesarean section is present, and such patients must be delivered abdominally. Under such circumstances the additional risk cannot be avoided, but it should be emphasized again that cesarean section should not be done simply for cardiac disease. Nor should cesarean section be done in order that sterilization may be performed. It is much safer to permit the cardiac patient to deliver vaginally and to return subsequently for sterilization, when sterilization is indicated and acceptable.

Approximately one-third of the patients who fall into class 3 will suffer decompensation at some time during pregnancy. If the patient presents herself early in pregnancy, the question of therapeutic abortion must be considered. This is a decision which the physician must make, provided that religion and the desire for a child do not contraindicate such an interruption. A history of previous heart failure, irrespective of whether this occurred during pregnancy or independently of pregnancy, represents a definite and urgent indication for therapeutic abortion, since 2 out of 3 such patients will decompensate if permitted to continue their pregnancy.

A second factor of major importance is the age of the patient. Cardiac patients over 35 years of age show a marked increase in the incidence of failure, and age alone in a class 3 patient is a definite indication for therapeutic abortion. Interruption of pregnancy in class 3 patients is relatively safe during the first trimester of pregnancy. This may be carried out by simple dilatation and curettage. After the first trimester, interruption of pregnancy is rarely indicated. It is usually safer to carry

such patients under adequate hospitalization and continue medical care than to interrupt the pregnancy after the third month. During the second trimester of pregnancy, when interruption seems essential, the safest method is abdominal hysterotomy under local anesthesia, at which time tubal ligation is desirable. Interruption of pregnancy is always hazardous, because such intervention adds to the existing circulatory load which is the greatest between the fifth and the eighth month of pregnancy.

The interruption of pregnancy during decompensation is extremely hazardous and is fatal in the majority of instances. Cardiac compensation must be re-established before any attempt at uterine evacuation. If such compensation is re-established there is rarely an indication for interruption of pregnancy in the second or third trimester. If the heart is decompensated, interruption cannot be safely performed, and if compensation is well established, interruption is rarely, if ever, indicated.

Class 4—Patients in class 4 are in heart failure. The treatment, then, is essentially the treatment of cardiac failure. Delivery by any known method carries a maternal mortality rate of more than 50 per cent and must be avoided if possible. Treatment of heart failure in pregnancy is a medical problem, the main objective of which is the restoration of cardiac compensation.

Myocardial Infarction — An Evolutionary Process

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MUCH has been said and written about the importance of "timing" in military and political affairs. The time element is just as important in medicine, both in diagnosis and in treatment. The physician is often tempted, when anxious relatives are pressing him for a diagnosis, to offer an opinion without waiting until all the necessary evidence is in. In a full-blown case of measles or chickenpox or herpes zoster it is easy and desirable to "pronounce" the disease, as the layman used to say, immediately. In a patient with obscure symptoms, however, several days may elapse before an accurate diagnosis can be reached—even after careful questioning and physical examination, supplemented by laboratory studies.

An excellent example of the importance of the time element in diagnosis is the average myocardial infarction. The clinician who looks on a coronary occlusion as a sort of evolutionary process which takes from one to three days to unfold, and who does not allow anxious and excited relatives to prod him into an immediate answer to the question, "What's the matter, doctor?" will not be embarrassed nearly so often as the physician who attempts to label every pain in the chest and upper portion of the abdomen within 10 minutes after he walks into the sick room.

Too many textbooks describe myocardial infarction as being characterized by substernal pain, fever, leukocytosis, an increased sedimentation rate, a precipitate fall in blood

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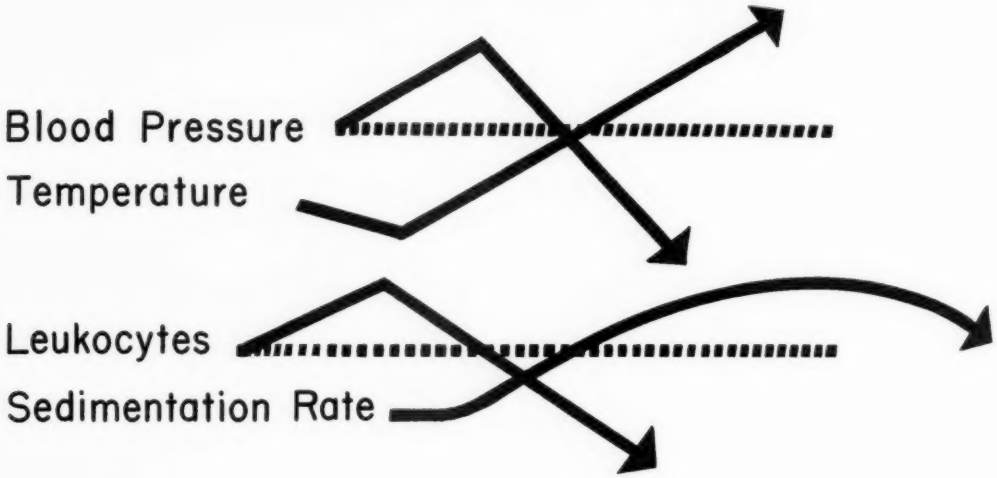

FIGURE 1. The evolution of the physical and accessory clinical findings following myocardial infarction.

TABLE 1

ONSET AND DURATION OF SYMPTOMS AND SIGNS OF MYOCARDIAL INFARCTION

	ONSET	DURATION
Pain	Immediate	2 to 48 hours
Fall in blood pressure	4 to 24 hours	Indefinite
Fever	24 to 36 hours	2 to 5 days
Friction rub (20-25 per cent)	2 to 36 hours	1 hour to 4 days
Leukocytosis	6 to 12 hours	2 to 4 days
Increased sedimentation rate	2 to 3 days	3 to 6 weeks
Electrocardiographic changes	2 to 72 hours	Indefinite

pressure, a pericardial friction rub and electrocardiographic changes. The impression may be left on the mind of the student—and may persist for some years in practice—that almost immediately after the onset of the pain the blood pressure falls, the temperature rises, the number of white blood cells and the sedimentation rate increase, and electrocardiographic changes develop. It is generally recognized that the friction rub is a much less constant sign, and is much oftener absent than present.

To have this textbook picture in mind as typical of a myocardial infarction is to miss many diagnoses. Except in massive infarctions, the blood pressure is more often elevated for the first few hours—perhaps for 24 to 36—after the onset before it begins to fall. The temperature seldom rises until at least 12, and oftener 24 to 36, hours have elapsed. Leukocytosis comes on early, within a few hours, but the sedimentation rate seldom rises for at least 24, and often 48, hours. The elevation persists for days or even weeks, while the leukocyte count returns to normal in the uncomplicated case within two or three days. The friction rub is to be heard in only 1 of every 4 or 5 cases, and may disappear within a few hours. Finally, the electrocardiographic changes may not appear for a day or two—sometimes four or five.

Table 1 and Figure 1 illustrate the order of appearance of the symptoms, signs and accessory clinical findings in the average moderately severe case of myocardial infarction. It will be noted that the first four symptoms and signs in the table are those which could be elicited at the patient's bedside, without any laboratory aids. The last three include two simple laboratory tests and the electrocardiogram.

Pediatrics IN GENERAL PRACTICE

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Use of Mineral-Enriched Meats as a Substitute for Milk in Various Clinical Conditions

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ALTHOUGH milk has long been accepted as the ideal food for infants and growing children, it is recognized that a small percentage of individuals in these age groups represent exceptions to the rule. For various reasons they are unable to take milk. Allergy to milk proteins is a familiar example of such an idiosyncrasy. It is well known that the ingestion of cow's milk by infants who are allergic to it may excite attacks of eczema, bronchial asthma or severe anaphylactic shock. Even death may result in an extremely hypersensitive infant. This allergic group of children requires a suitable substitute for milk in order to avoid untoward reactions and, at the same time, to permit normal growth and development.

One of the most interesting clinical conditions in which some other complete food must be given in the place of milk is galactosemia, in which there is a congenital inability to metabolize the sugar, galactose, derived from the lactose in milk. The liver, which becomes enlarged by infiltration with fat,[1,2] is probably the site of this defect. However, not all galactose metabolism occurs in the liver.[2,3]

Other clinical features which characterize this metabolic disorder in its fully developed form are (1) retarded or arrested physical growth and development, (2) formation of cataracts, (3) albuminuria, (4) galactosuria and (5) feeblemindedness, when milk feeding is persisted in. All these serious complications can be avoided if galactose (milk) is eliminated from the diet at a very early age.

For many children who dislike milk, and so do not take enough to satisfy their basic requirements for calcium, provision of a suitable milk substitute containing this element is desirable for supplementation of their customary diets. The treatment of epilepsy by means of a ketogenic diet excludes the use of fresh milk because of its comparatively high lactose content. In some parts of the world milk is entirely unavailable to large sections of the child population, making a substitute mandatory if normal nutrition is to be maintained.

The present experimental and clinical studies were designed to compare the nutritive value of cooked lean meat, properly enriched with calcium, phosphorus, magnesium, trace elements and certain vitamins, with that of

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whole cow's milk as a principal source of protein and minerals in the diets of growing rats and children. From the viewpoint of calcium retention, such a diet would appear to be superior to those depending on vegetables for their sole source of this element.

Our investigation consisted of two parts: (1) a fairly extensive experimental study relating to the effects of various diets on the utilization of calcium and phosphorus and on the total body growth of rats and (2) balance and growth studies on older children and infants receiving a milk substitute in their diet. The details regarding the methods employed in the animal study have been described in earlier reports.[4,5]

Animal Experiments

The results of various phases of the study are best presented with the aid of a series of graphs and tables, which summarize the detailed data. Although all experimental data, excepting those on the serum of rats, were obtained for individual animals, group averages alone are represented to save space. Variations in individual responses within the groups were not sufficiently significant to justify reporting the individual data.

Growth curves of young rats maintained on the mineral-enriched meat diet are shown in Figure 1, for comparison with those of control animals fed a diet in which milk was the sole source of protein, calcium and phosphorus. Curves for males and females are presented separately. Each line is a composite growth curve for a small group of animals. Only among the meat-fed male animals does one group appear to outstrip the others significantly in growth. No explanation for this difference is apparent. It is obvious that the growth of the meat-fed rats, receiving a portion of their carbohydrate as added lactose, is inferior to that of both the milk-fed and the other meat-fed animals. The mechanism of this deleterious effect of lactose is obscure. Other workers have reported a species intolerance on the part of the rat to artificially prepared lactose. However, comparison of the average growth curves of rats fed the meat diet (exclusive of those receiving lactose) with those on the milk diet indicates no superiority of the latter. In fact, meat-fed rats grew at a slightly greater rate than the milk-fed rats.

The results of analyses of the pooled blood serum of the various groups of meat-fed and milk-fed rats were all considered normal. Aver-

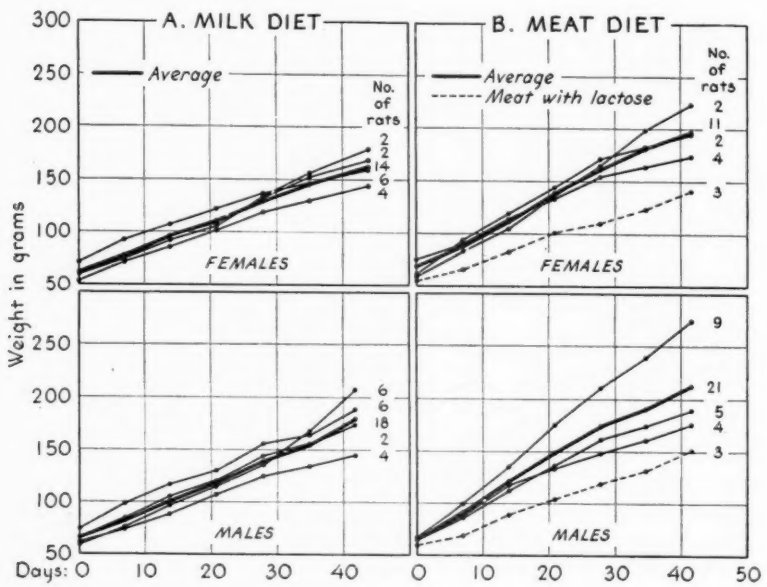

FIGURE 1. Growth curves of rats reared on: A. milk diet; B. basic meat diet, similar composition.

TABLE 1*

WHOLE CARCASS ANALYSES OF RATS REARED ON (A) MILK DIET AND (B) MEAT DIETS OF SIMILAR COMPOSITION

DIET	NUMBER OF RATS	BODY WEIGHT (grams)	PER CENT OF WET BODY WEIGHT			PER CENT OF ASH	
			Ash	*Calcium*	*Phosphorus*	*Calcium*	*Phosphorus*
FEMALES							
Milk	12	151	4.09	1.21	0.69	29.41	17.00
Meat	6	187	3.85	1.12	0.59	29.08	15.22
Meat with lactose	3	120	3.77	1.07	0.63	28.38	16.71
MALES							
Milk	11	174	3.94	1.10	0.61	27.95	15.66
Meat	10	191	3.47	1.06	0.57	30.70	18.20
Meat with lactose	3	130	3.88	1.10	0.64	28.35	16.49
MALES AND FEMALES							
Milk	23	162	4.01	1.15	0.65	28.71	16.35
Meat	16	189	3.61	1.08	0.58	30.09	17.08
Meat with lactose	6	125	3.82	1.08	0.63	28.36	16.60

*From McQuarrie and Ziegler.[4]

age values for all the animals in the two separate categories show no significant difference between them.

Whole carcass analyses of litter mate rats reared on either the milk type of diet or the mineral-enriched meat diet were made according to methods previously outlined elsewhere.[4,5] The results are presented in Table 1. The meat-fed rats were divided into two groups because those which received a portion of their added carbohydrate in the form of lactose did not grow as well as those not receiving this sugar (Figure 1). Figures recorded for the different groups are the averages of all individual analyses in those groups. Because of the possible differences due to sex, such as body size, data for males and for females are tabulated separately.

The body weights of animals on the mineral-enriched meat without lactose were consistently higher than those fed the milk diet, but the percentages of total ash and calcium in the wet carcass tended to be only slightly higher on the average in the milk-fed animals. While the meat-fed rats which received lactose were significantly lighter in weight than the other animals, the percentages of total ash, calcium and phosphorus were of the same magnitude. It is fair to interpret these data as indicating little or no important metabolic differences between the milk-fed and the modified meat groups, except for the slowed rate of growth of the meat-fed rats which received lactose.

Additional evidence of the comparative value of the mineral-enriched meat diet and the milk diet was obtained by evaluating the calcium, phosphorus and organic matter found in the femurs of rats from each experimental group. A series of studies was carried out to determine whether some calcium-phosphorus ratio other than that in milk (1.36/1) might alter the nutritional value of the meat diet. It has appeared that a moderate decrease as well as a significant increase in phosphorus level compared with that of milk may be compatible with a suitable rate of growth under the conditions of this experiment. Animal experiments were also conducted which showed that it is necessary throughout the period of growth to add both calcium and phosphorus to the diet in amounts far greater than those

in unenriched meat. These feeding experiments with rats, using a mineral-enriched meat substitute comparable to that of cow's milk, proved that the meat diet was equal in all respects to the milk diet.

Mineral-Enriched Meat Formula for Infants

From these findings in rats several recipes have been formulated for feeding infants and young children, using cooked and strained lean meat fortified with fat, carbohydrate, certain vitamins, and calcium, phosphorus and magnesium salts.

A typical formula for use as a substitute for 500 gm. (about 1 pint) of whole cow's milk is given in Table 2. The composition differs somewhat from the original formula previously recommended.[4] The alteration is due largely to a variation in the percentage composition of the protein and salts in the strained beef used (Swift's baby meats).

To make a smooth homogeneous formula in which the meat remains in fine suspension until fed, follow the directions given below for home preparation.

When this formula is to be prepared in the home, a fair approximation of the weighed constituents used in our experiments can be obtained by employing household measurements as follows and mixing with a WARING BLENDOR or a rotary egg beater after adding each part of the recipe (B, C, D and E).

A. Rice, dry ..... 1 heaping tablespoon
Water ..... 1 cup
Cook in a double boiler until the rice is very soft; put through a fine sieve if a blendor is not available; transfer to a mixing bowl; add components listed in B.

B. Strained beef* ..... ½ cup
DEXTRI-MALTOSE® ..... 2 tablespoons
Lard ..... 1 tablespoon
Salt mixture I A (calcium gluconate) ..... 1 tablespoon
or
Salt mixture II A (veal bone ash) ..... ½ teaspoon

C. Salt mixture I B or II B (Table 2) in 1 ounce of water

D. Water to bring the total volume to one pint

E. Vitamins to satisfy the nutritional needs of the child

*Swift & Company.

The salts can be obtained in any pharmacy. It is desirable to have the pharmacist make up 32 times the weight of each salt listed either as I B or II B in Table 2 in one quart of water. The resulting suspension should be thoroughly mixed just before it is measured. One ounce of the salt mixture is used for each pint of formula.

Veal bone ash has been used as the principal source of calcium with good results. It was considered a more complete mineral supplement for the recipe because of the possible nutritional significance of the trace elements which it contains as well as calcium and phosphorus. The importance of traces of copper, zinc, fluorine and manganese, which are contained in the bone ash, is already fully recognized by nutritionists. Other trace elements which are contained in veal bone ash may be proved of value in nutrition in the future.

In most of our diets strained beef has been preferred for the younger children. However, it is possible to substitute strained lamb or strained liver without materially altering the protein content (lamb 13.12 per cent, beef 13.44 per cent and liver 13.51 per cent) of the milk substitute; the fat and mineral content requires a slight adjustment. If strained pork is used, the protein (15.11 per cent) and fat (6.49 per cent) intakes are slightly higher than from the same amounts of beef. The chopped meats have been employed to advantage for older children. The younger experimental subjects have been more cooperative, however, on a liquid formula in which strained meats have been utilized.

The mineral-enriched meat formula has been used to advantage in the following clinical cases: 6 cases of allergy to milk proteins, 1 case of galactosemia, 2 cases of epilepsy, 2 cases of familial hypoglycemia, 3 cases of lipoid nephrosis, 1 case in which the child could not fabricate serum proteins in a normal manner, 1 case of familial periodic paralysis, 1 patient with residual partial paralysis from poliomyelitis, 1 patient with progressive muscular dystrophy, 1 with pituitary dwarfism and a number of children hospitalized for various other clinical conditions.

All the patients thrived on the enriched

meat diet. Balance studies were carried out in 8 of the cases to determine the degree of utilization of the mineral-enriched meat diet in children. The results are shown in Table 3. In connection with the case of galactosemia other pertinent tests, such as glucose and galactose tolerance tests, were performed in order to determine the relative value of the enriched meat diet.

Space does not permit an analysis of results in all the cases. This should be quite unnecessary because of the similarity of the end results in all types observed for a considerable period of time. For this reason only 2 patients are considered here in detail. One of these was an infant who was highly allergic to milk protein; the other, also an infant who had galactosemia.

Case 1 (allergy to cow's milk)—A 2½ month old male infant was admitted to the University of Minnesota Hospital on October 7, 1949, with a history of diarrhea almost since birth. He had not gained weight normally. The birth weight was 2,874 gm. The infant was breast fed for two weeks, after which time the mother's milk became unavailable because of mastitis. During this period of breast feeding the patient's stools were apparently normal. A formula of whole cow's milk, water and dextri-maltose was then given every four hours. The infant took about 3½ oz. at a feeding, but within 10 to 15 minutes after each feeding, projectile vomiting occurred. Within two weeks the patient began to have 15 to 20 watery stools daily, at times streaked with blood. The feeding was changed first to evap-

TABLE 2

COMPONENTS OF MINERAL-ENRICHED MEAT FORMULA (EQUAL IN AMOUNT TO THOSE OF 500 GM. WHOLE COW'S MILK)

CONTENTS	PROTEIN (gm.)	FAT (gm.)	CARBOHYDRATE (gm.)	CALCIUM (mg.)	PHOSPHORUS (mg.)	SODIUM (mg.)	POTASSIUM (mg.)	MAGNESIUM (mg.)	CHLORINE (mg.)
Beef, strained* (120 gm.)	16.1	5.0		13.2	108.0	238.8	253.2	13.0	325.2
Rice, 16 gm.	1.3	0.04	12.6	1.7	15.5	0.3	20.9	5.2	8.6
Lard, 14.5 gm.		14.5							
Dextri-maltose, 12 gm.			11.8						
Salt mixture, I or II				575.7	340.4	10.9	426.0	42.3	190.7
Water, to make 500 gm.									
Vitamins†									
TOTALS	17.4	19.5	24.4	590.6	463.9	250.0	700.0	60.5	524.5

*Swift & Co.

†To meet full nutritional requirements.

SALT MIXTURE I

		Grams
A.	Calcium gluconate	6.44
B.	K Cl	0.4009
	K_2CO_3	0.3814
	$(MgCO_3)_4\ Mg(OH)_2\ 5H_2O$*	0.1630
	$NH_4H_2PO_4$	1.2121
	$Na\ H_2\ PO_4\ H_2O$	0.0654

*U.S.P. XI.

SALT MIXTURE II

		Grams
A.	Veal bone ash*	1.515
B.	K Cl	0.3997
	K_2CO_3	0.3822
	$(MgCO_3)_4\ Mg(OH)_2\ 5H_2O$	0.1334
	$NH_4H_2PO_4$	0.2551

*Mead Johnson and Company.

TABLE 3

NITROGEN, CALCIUM AND PHOSPHORUS BALANCES IN VARIOUS CLINICAL CONDITIONS, WHILE THE PATIENT RECEIVED A MINERAL-ENRICHED MEAT DIET

CASE	AGE	DIAGNOSIS	DIET	NUMBER OF DAYS	SODIUM (gm.)	CALCIUM (gm.)	PHOSPHORUS (gm.)
1	2½ mo.	Allergy to milk	Meat	9	+2.23	+0.280	+0.284
2	2 mo.	Galactosemia	Meat	7	+0.82	+0.088	+0.095
			Milk	11	+0.64	+0.112	+0.054
3	13 yr.	Epilepsy	Meat	4	+7.05	+0.317	+0.143
4	10 yr.	Pituitary dwarf	Meat	14	+2.35	+0.434	+0.256
5	3 yr.	Hypoglycemia	Meat	11	+1.79	+0.150	+0.108
			Milk	11½	+1.82		+0.156
6	4½ yr.	Hypoglycemia	Meat	11	+2.49	+0.337	+0.232

orated milk and then to a commercial formula designed to simulate human milk, but without improvement in the gastrointestinal symptoms.

Examination revealed a somewhat cachectic little boy weighing 3,859 gm. and looking acutely ill, with a markedly distended abdomen, no subcutaneous fat, poor color of skin and mucous membranes, and a weak cry.

At the outset he was given the nursery milk formula but the abdomen remained distended. Under these conditions the lower portion of the large bowel was found to be normal when examined by means of proctoscopy and a barium enema. A roentgenogram of the abdomen showed abnormal gaseous distention of both large and small intestines. Laboratory examinations for parasites and abnormal enzyme activity were negative. Although the skin test for sensitivity to milk was negative, the number of eosinophils in the stool increased; diarrhea and regurgitation of feedings continued, suggesting milk allergy.

The feedings were changed to NUTRAMIGEN®, a protein hydrolysate and carbohydrate mixture. A fair weight gain was then made but the abdomen remained distended. A more or less empiric test for intestinal allergy was carried out as follows while the patient was on the milk-free diet: A feeding of cow's milk formula was given following an overnight fast; a differential white blood cell count and an absolute eosinophil cell count were made before and repeated at intervals after the meal. A marked increase in total white blood cell and eosinophil counts occurred in 40 minutes (white blood cells 10,750 to 16,300; eosinophils 302 to 447). This response was thought to be more than that expected from a meal in a nonallergic infant.

On the basis of these tests and the patient's symptoms, a tentative diagnosis of intestinal allergy to milk was made and the infant was fed the meat formula already described. Improvement in the patient's clinical condition was very striking. During succeeding weeks he made a satisfactory gain in weight. A balance study covering a period of nine days was carried out during the latter period to evaluate the degree of utilization of nitrogen, calcium and phosphorus. The results are shown in Table 3. The infant was then discharged to his mother on the meat formula, weighing 6,060 gm. Within five months his weight had increased to 8,850 gm. There was no diarrhea and the development was normal. The patient was continued successfully on the meat formula supplemented with vegetables and fruits.

Case 2 (galactosemia)—A white female infant was first seen at the University Hospitals at the age of 2 months. She was jaundiced and had failed to gain weight since birth. The jaundice which had developed on the fourth day of life persisted for a number of weeks. (The mother, father and baby were all Rh

positive.) Blood cultures were sterile. Since her sixth week of life the hemoglobin had fallen steadily and her jaundice had increased. She was irritable, slept little, was constipated and had considerable pain on defecation.

Physical examination revealed a rather small but fairly well developed and moderately well nourished infant weighing 3,550 gm. The head circumference was 35.5 cm., chest 33.5 cm., body length 46 cm. There was only slight icterus. The eyes showed lenticular opacities. The diagnosis of lenticonus was also considered by a member of the staff in ophthalmology. The chest was clear to auscultation and percussion. The heart size and action were within normal limits. Abdominal examination showed an enlarged liver with a firm, rather sharp edge 5 cm. below the costal margin in the midclavicular line on the right, and 3 cm. below in the midclavicular line on the left. The spleen was not enlarged. The genital and rectal examinations were negative.

Initial laboratory tests showed the urine to have a specific gravity of 1.008 with albumin 1+ and sugar +. Microscopic examination was negative for casts and blood cells. The slight jaundice, hepatomegaly, albuminuria, melituria and lenticular opacities suggested a diagnosis of galactosemia. The reducing substance in the urine was identified as galactose. The fasting blood specimen contained 67 mg. of nonfermentable sugar per hundred milliliters, identified as galactose.

Hemoglobin was 10 gm. per hundred cubic centimeters, red blood cells 3.28 million per cubic millimeter and leukocytes 7,923 per cubic millimeter with neutrophils 23, lymphocytes 74 and monocytes 3 per cent. During the period of hospitalization the child first received a milk formula which was later changed to a mineral-enriched meat diet. Galactose and glucose tolerance tests were carried out, as well as mineral and nitrogen balance studies under both dietary regimens.

The results of the balance studies on milk and on meat are shown in Table 3. Although there appears to be little difference in the retention of the various elements during the two dietary periods, the child showed marked clinical improvement with an amazing change in her activity and in her disposition after the mineral-enriched strained meat formula was substituted for the previous milk diet.

The clinical improvement was correlated

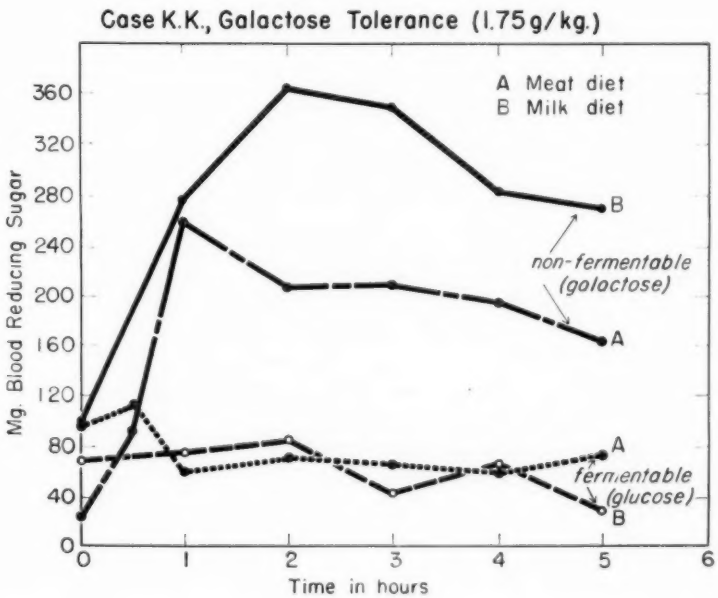

FIGURE 2. Galactose tolerance test, showing decrease in fasting value of blood galactose and a corresponding increase in the fasting blood glucose, as well as a lower galactose tolerance curve during meat feeding period.

with the decrease in her circulating blood galactose. Why galactosemia should cause such a marked change in the infant's condition is not understood. It may well be that galactose has a direct deleterious effect on the body metabolism as Bruck and Rapoport[6] have suggested.

A comparison of the galactose tolerance test curves present in Figure 2 shows a decrease in the fasting value of blood galactose and a corresponding increase in the fasting blood glucose as well as a lower galactose tolerance curve during the meat feeding period.

The finding of galactosemia for five weeks after omission of galactose from the diet was unexpected. This delay in its removal suggests not only impaired ability to oxidize or convert it but also the possibility of impaired urinary excretion.

Two hypotheses have been advanced to explain the symptoms of galactosemia. The first, suggested by Mason and Turner,[7] considered the condition to be due to an inability of the body tissues to convert galactose to glucose. The resulting galactosemia, according to this view, produces a hypoglucosemia with subsequent glucose starvation. Bruck and Rapoport[6] held that the low blood sugar played no part in the symptomatology because it was not a constant finding. Moreover, hyperinsulinism and glycogen storage disease (von Gierke type), both of which exhibit hypoglycemia, do not cause symptoms identical with those of galactosemia. The latter authors thought that galactose itself may have a toxic effect.

Galactose tolerance tests were performed on both the mother and the father of our patient. Both parents showed abnormally high blood galactose curves which did not return to the fasting level before the end of the second hour. The galactose index for the mother was over 110 and that for the father was over 190. Since the average normal value of the index is 68 and the upper limit of normal 160, these results indicated a definitely reduced galactose tolerance in the case of the father. These findings in the parents tend to substantiate the existence of an hereditary factor in galactosemia, as discussed by Donnel.[2]

At present the diets given to patients with galactosemia as substitutes for milk have been nutramigen, a mixture of a protein hydrolysate and nongalactose-containing sugars, CASEC® (calcium caseinate) and soybean preparations. While galactosemia is not a common disorder, it occurs more frequently than the literature implies.[8] Lean meat products supplemented with calcium and other essential ingredients should prove to be most useful in the diets of children suffering from this disease.

Summary

1. Experiments on the nutritive value of cooked lean meat supplemented with calcium and other ingredients, as compared with whole cow's milk, have been reviewed.

2. Rats fed the mineral and vitamin-enriched meat diet, constructed to simulate whole milk, thrived on the same. As measured by body weight gains and carcass analyses, they differed in no significant way from litter mate control animals which received milk as a basis of the diet.

3. Infants and young children suffering from a variety of clinical disorders were also found to thrive on the milk-free, mineral-enriched meat diet.

4. The latter diet was shown to be quite superior to a milk diet for one infant with severe allergy to cow's milk and for one suffering from congenital galactosemia. Reports of these 2 patients are presented in detail.

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Significance of Hepatomegaly in Infants and Children

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ENLARGEMENT of the liver occurs in infants and children for many reasons. It may be an isolated finding or it may be associated with other abnormal signs such as jaundice and splenomegaly. Himsworth[1] has pointed out that it is usually produced in one of six ways: (1) engorgement with blood, (2) engorgement with bile, (3) inflammation, (4) hyperplasia, (5) infiltration and (6) new growths.

Apparent enlargement may be due to forward and downward displacement of the liver and to its normal position, making it palpable in infants and young children.

In some instances, the cause of enlargement is obvious. In other instances, it is obscure and may not be determined if one is not aware of the possibilities.

To facilitate such an awareness and to offer a guide in differential diagnosis, most of the causes of hepatomegaly in children are listed in Tables 1 to 4, which are arranged on the basis of the simultaneous absence or presence of splenomegaly and jaundice. The causes of hepatomegaly in infancy are also given (Table 5). Under each main heading, subdivisions are made according to a modified outline by Himsworth. When the facts in the history of a patient are considered in relation to objective signs, a correct diagnosis often can be strongly suspected or made. Properly chosen laboratory tests are then useful in helping to establish the true nature of the condition.

It can be seen that a complete blood cell count and examination of a stained blood film for morphologic changes will help prove the presence or absence of many of the diseases in question. A roentgenologic study of the thorax is helpful if one suspects the presence of a lesion of the heart or of the lungs. A flocculation test or complement fixation test for syphilis should always be done.

It may be necessary to perform one or more of the so-called liver function tests. No one of these can measure all of the functions of the liver. All are of limited usefulness. The liver may be affected extensively by disease but the results of many, if not all, of the currently available tests of hepatic function may be normal. This is especially true in children in whom the liver is the site of metastatic malignant disease, or the site of cystic and other changes which do not produce generalized hepatocellular destruction. Much has been written about "hepatograms"[2] and "liver profile" and "liver function schedules"[3]—groups of liver function tests each of which is

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TABLE 1

CAUSES OF HEPATOMEGALY ALONE

A. Apparent enlargements and anomalies
   1. Normal but palpable
   2. Deformed thoracic wall and displaced liver
   3. Emphysema
   4. Pneumothorax
   5. Right-sided pleural effusion
   6. Hepatoptosis
   7. Riedel's lobe (rare)
B. Engorgement with blood
   1. Heart failure
      a. Congenital heart lesion
      b. Paroxysmal tachycardia
      c. Rheumatic heart disease
   2. Adhesive pericarditis (Pick's disease)
C. Engorgement with bile
D. Inflammation
   1. Syphilis
   2. Abscess of liver
      a. Amebic
      b. Pyogenic
   3. Actinomycosis
   4. Tuberculosis
   5. Malaria
   6. Hepatitis (acute)
   7. Miscellaneous infections
E. Hyperplasia
   1. Cirrhosis
   2. Chronic hepatitis
   3. Hepatolenticular (Wilson's) disease
F. Infiltration and storage
   1. Von Gierke's disease
   2. Amyloid, secondary. Primary very rare
   3. Fatty infiltration (steatosis)
      a. Primary (?)
      b. Secondary to diabetes
      c. Selective starvation
   4. Reticuloendotheliosis
      a. Schüller-Christian disease (not common for liver only to be enlarged)
      b. Letterer-Siwe disease
   5. Galactosemia
   6. Leukemia
   7. Fanconi syndrome (cystinosis)
   8. Diabetic coma
G. New growths
   1. Metastatic cancer, including lymphosarcoma
   2. Primary cancer
      a. Hepatoma
      b. Mixed tumor
   3. Angiomas
   4. Cysts
      a. Hydatid
      b. Alveolar
      c. Cystic disease
   5. Hemangioendothelioma (rare)
   6. Hamartoma

presumed to measure a different function. A detailed discussion of these tests is beyond the scope of this paper. All of them can be carried out in infants and children. My colleagues and I usually make one or more of the following determinations: (1) sulfobromophthalein excretion (only in nonicteric patients), (2) amount and type of bilirubin in the blood, (3) bile (qualitatively) and urobilinogen (quantitatively) in the urine, (4) flocculation reactions (cephalin-cholesterol, thymol turbidity, and zinc sulfate turbidity), (5) blood plasma proteins and the albumin-globulin ratio, (6) blood sugar, (7) blood prothrombin time, (8) alkaline phosphatase in the blood, (9) cholesterol and cholesterol esters in the blood and (10) glucose tolerance. It is not necessary to do all of these tests in every child who has hepatomegaly.

The sulfobromophthalein (BROMSULPHALEIN®) test is employed probably more than are the others. We have not employed it in new-

TABLE 2

CAUSES OF HEPATOMEGALY ASSOCIATED WITH SPLENOMEGALY AND JAUNDICE

A. Apparent enlargements and anomalies
B. Engorgement with blood
C. Engorgement with bile
   1. Obstruction of bile ducts
      a. Congenital
      b. Mucous plugs
D. Inflammation
   1. Syphilis
   2. Acute hepatitis
   3. Infectious mononucleosis
   4. Weil's disease (leptospirosis)
   5. Toxoplasmosis (rare)
   6. Poisonings (liver may be small instead of enlarged)
E. Hyperplasia
   1. Cirrhosis
   2. Chronic hepatitis
F. Infiltration
   1. Erythroblastosis
   2. Hemolytic anemia
      a. Congenital
      b. Acquired
   3. Leukemia
   4. Sickle cell anemia
G. New growths
   1. Cancer, including lymphosarcoma

TABLE 3

CAUSES OF HEPATOMEGALY ASSOCIATED WITH SPLENOMEGALY WITHOUT JAUNDICE

A. Apparent enlargements and anomalies
B. Engorgement with blood
C. Engorgement with bile
D. Inflammation
   1. Infectious mononucleosis
   2. Syphilis
   3. Malaria
   4. Tuberculosis
   5. Sometimes associated with subacute infections of respiratory tract
   6. Histoplasmosis
   7. Toxoplasmosis
E. Hyperplasia
   1. Cirrhosis
   2. Chronic hepatitis
   3. Portal hypertension (liver may be of normal size and not affected)
F. Infiltration and storage
   1. Leukemia
   2. Storage diseases
      a. Niemann-Pick
      b. Gaucher's
   3. Reticuloendotheliosis
      a. Schüller-Christian (not a very common feature of disease)
      b. Letterer-Siwe
   4. Amyloid disease (not common)
   5. Osteopetrosis (Albers-Schönberg disease)
G. New growths
   1. Hodgkin's disease

TABLE 4

CAUSES OF HEPATOMEGALY ASSOCIATED WITH JAUNDICE WITHOUT SPLENOMEGALY

A. Apparent enlargements and anomalies
B. Engorgement with blood
C. Engorgement with bile
   1. Obstruction of bile ducts
      a. Congenital anomaly
      b. Mucous plugs
      c. Ascaris and other worms
D. Inflammation
   1. Abscess of liver
      a. Amebic
      b. Pyogenic (sometimes)
   2. Syphilis
   3. Acute hepatitis
   4. Serum hepatitis
   5. Weil's disease
   6. Yellow fever
   7. Septicemia
   8. Tuberculosis (if nodes obstruct common duct)
   9. Poisonings (as carbon tetrachloride, mushroom) —acute necrosis, liver may be small
E. Hyperplasia
F. Infiltration
G. New growths
   1. Cysts
      a. Hydatid
      b. Alveolar
   2. Hodgkin's disease (if nodes obstruct common duct)
   3. Cancer (occasionally)
      a. Hepatoma
      b. Mixed tumors

born infants, though Yudkin and Gellis[4] report that its use is feasible. They state that there is retention of as much as 23 per cent of the dye after 45 minutes in normal infants up to the age of 4 days. Fever will result in transient retention of the dye in most patients,[5] as will cardiac decompensation. Normally, there should be no retention of dye at the end of one hour, which is the standard time for obtaining the second blood specimen in our institution.

The normal values for the flocculation tests in adults are the same as those obtained in children although the values for the zinc sulfate turbidity test may be slightly lower in children. In normal newborn infants, the cephalin-cholesterol flocculation test may give positive results.[6] In undernourished children in whom values for plasma proteins are low, the results of the flocculation tests are unreliable.[7] Values for bilirubin, protein, sugar and prothrombin in the blood are the same for children as for adults. In the newborn period, there is some increase in the value for bilirubin[6] and sometimes decrease in the values for protein,[6] cholesterol[6] and sugar.[8]

In some situations bone marrow must be examined. Occasionally, needle biopsy of the liver is necessary. Sometimes one must resort to surgical exploration and direct biopsy in order to be certain of the diagnosis.

It should be pointed out that certain conditions are more likely to be encountered than are others. Geographic area, local conditions and, under some circumstances, race of the patient will determine the diseases more likely to be encountered. In our experience, palpable but normal livers, both acute and chronic hepatitis, portal hypertension, congenital obliteration of the bile ducts, erythroblastosis and leukemia have been those more commonly encountered.

These comments can in no way be construed

TABLE 5

CAUSES OF HEPATOMEGALY IN INFANCY

A. Apparent enlargements and anomalies
   1. Normal but palpable liver (right lobe only may be palpable)
   2. Hepatoptosis
B. Engorgement with blood
   1. Heart failure
      a. Congenital heart disease
      b. Paroxysmal tachycardia
C. Engorgement with bile
   1. Obstruction of bile ducts
      a. Congenital obliteration
      b. Mucous plugs
D. Inflammation
   1. Septicemia
   2. Syphilis
   3. Histoplasmosis
   4. Cytoplasmic inclusion disease
   5. Infantile hepatitis
E. Hyperplasia
F. Infiltration and storage
   1. Erythroblastosis
   2. Storage diseases
      a. Niemann-Pick
      b. Gaucher's
         (1) Acute
         (2) Chronic
   3. Von Gierke's disease
   4. Galactosemia
   5. Fanconi (cystine storage) syndrome
   6. Letterer-Siwe disease (reticuloendotheliosis)
   7. Leukemia (rare)
   8. Osteopetrosis (rare)
   9. Toxoplasmosis (rare)
G. New growths
   1. Hemangioendothelioma (rare)
   2. Cancer (very rare)
      a. Primary
         (1) Hepatoma
         (2) Mixed tumor
      b. Secondary
         (1) Metastatic neuroblastoma

as a complete discussion of the differential diagnosis of hepatomegaly in infants and children nor of the various laboratory procedures mentioned. They are offered only as a brief guide to the solution of problems which may be very puzzling.

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THE NONSURGICAL PROLONGATION OF LIFE

ADVANCES in surgical technics, along with perfections in anesthesiology and preoperative and postoperative management, have reduced the operative mortality of certain operations from the prohibitive figures of a decade ago. Cancer that used to be considered inoperable is now being attacked with renewed vigor and the crises that follow operation are being successfully met by the well trained staff and the well equipped hospital. Now there is a rising tendency to attempt the impossible, to restore the terminal cancer patient to health. The reasons for such efforts are well founded in the attitudes of all concerned, except maybe the patient himself. No matter how wasted, crippled and harassed the patient may be, the family looks upon the surgeon as capable of performing a miracle and of arresting the disease. With the rapid development in medical science, who knows what week may bring the definitive advance that will rob cancer of its terrors? The prolongation of life is, therefore, an important objective in submitting the patient to surgery, even when metastatic involvement is obvious.

The surgeon feels a certain duty to the patient and to the family to leave no stone unturned, no avenue unexplored, that may yield benefits. There are just enough reports of unexpectedly benign lesions, or of resolution and disappearance of metastatic lesions once the original tumor has been removed, to reinforce the decision of the surgeon to perform the operation. The factor of pressure by the family upon the surgeon cannot be minimized. If the surgeon acknowledges that the disorder has advanced too far to be curable, he may be requested to call a consultant. The family may even transfer the patient from his care to that of some other surgeon with a reputation for undertaking the most difficult problems. The family then feels that "everything has been done" and that their debt to the dying patient has been discharged.

If the proposed operation relieves the patient of suffering and distress it is to be commended. Too often, however, the operation is not even palliative. To visit the patient during the days after operation is not quite reassuring; needles in three of his four extremities, an oxygen mask or tent, a catheter, an airway, and very possibly a tracheotomy tube through which suction is applied at intervals. Fortunately, the patient is usually narcotized and only momentarily aware of the jabs of needles with antibiotics and other medications. If the patient survives the postoperative period, he has the prospect of early ambulation when he would probably much rather just pass out of the picture. Return home is another adjustment that may present difficulties. And within a matter of weeks, or a few months at the most, the patient enters the hospital again for terminal care.

In such a patient, palliative surgery has

probably prolonged life. But this is by no means always the case. The surgeon realizes that unless the areas of malignancy are completely removed, recurrence is inevitable. He is, therefore, tempted to go beyond the limits of prudence knowing that he will not have a second chance. The more conservative surgeon will consider that a live patient is better in any circumstances than a dead one, no matter how perfect the operation. Furthermore, even though evidence is strong that complete removal is impossible, opinion prevails that the patient deserves a last effort to save his life.

Deaths a few days after extensive operations on the head, thorax, abdomen, and pelvis are increasing rather than decreasing. Inordinately large numbers of erstwhile patients come to the autopsy table with dressings still in place and sutures unremoved. Postmortem examination does not always reveal the immediate cause of death. Postoperative hemorrhage, infection, and the like are sometimes quite evident. In other cases, the presence of untouched metastatic lesions in the liver, lymph nodes, and elsewhere testify to the inadequacy of the operation. When none of these is present, it must be assumed that the operation overtaxed the restorative powers of the patient. Maybe this was at the chemical level; but maybe it was at the psychologic level. Some patients with advanced cancer have lost the will to live. Mere discussion with the family physician or with the surgeon is seldom sufficient to restore to the cancer patient his will to live. The patient who looks the surgeon in the eye and says in substance: "Yes, Doctor, go ahead and operate on me, but I'll die anyhow," is usually accurate, even to the day. The surgeon is at a serious disadvantage in such cases.

The financial problem of the patient with advanced cancer deserves consideration. Here the self-restraint of the surgeon may save the family enough for the completion of the education of a patient's child, or furnish the bereaved with enough to keep him or her from being a financial burden upon children struggling to establish themselves. Hospital, nursing, and medical and surgical bills running into thousands of dollars mean considerable additions to the costs of medical care. Even when these costs are defrayed by participation in medical care programs, the costs are distributed but not reduced. They merely make for increased premiums for all the others.

It is unjustifiable to count the cost where saving of life is concerned, but when life is not saved, in fact when death is actually hastened by injudicious surgery, it seems hard to justify such a heroic remedy. The physician and the surgeon will find this situation an area for mutual development with the family and may be able in some cases to put across the idea of nonsurgical prolongation of life.

WALTER FREEMAN

DECLINE OF MORTALITY FROM RHEUMATIC FEVER

A DEFINITE decrease in the number of deaths from rheumatic fever, particularly among white children, has been taking place in recent years, even before the arrival of the miracle drugs ACTH and cortisone. The decrease in nonwhites does not compare with white adolescents. In an analysis of the mortality rates from every reasonable point of view, Dr. George Wolff,[1] eminent health research statistician, formerly of the Children's Bureau, reports results which indicate his belief that a certain hereditary factor plays a role in the development of rheumatic fever and probably also in the fatal outcome of the disease. His statement was made at a seminar conducted at St. Francis Sanatorium, Roslyn, Long Island, New York, in May 1952.

There is no exact way to determine the actual number of cases of rheumatic fever and its sequelae in our population. The disease is long drawn-out and has varying manifestations, recurrences and relapses. Although the dramatic end is often correctly diagnosed, the mild or incipient case is a diagnostic problem. The difference in crude rates for mortality from acute rheumatic fever plus heart diseases was somewhat greater than fourfold in the states—from 5.3 in Vermont to 22.4 in Utah. Exceedingly low rates were those of Vermont, California, Arkansas, Maine

and Kansas. Highest mortality rates were found in Utah, Delaware, Colorado, District of Columbia, New Jersey, Pennsylvania and New York.

Dr. Wolff points out the impressive decrease in mortality among white children—in the neighborhood of 80 per cent for the ages of 5 to 14 years and 70 per cent for older children. He reached the conclusion that the more unfavorable environment of nonwhite children tended to increase the risk of dying. The figures indicated an absolute death toll among all persons in 20 years amounting to 4000 annual deaths up to 1941, with a steady decrease since that time.

The final conclusion is that the progression of low rates in the Southern and Pacific states to significantly high rates in the Northern and especially the Middle Atlantic states points to the role of certain social economic influences in the environment as significant in the outcome of rheumatic fever in addition to the specific infective agent and social environmental factors.

Obviously the conclusions reached by Dr. Wolff in May 1952 are yet to be modified by the application of much knowledge that has been gained even since that time relative to advantages from administration of cortisone and ACTH, to use of salicylic acid products, to prevention of streptococcal infections, and to treatment of such infections by such products as the sulfonamides and antibiotics.

MORRIS FISHBEIN

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TRAUMA AND THE HAND

This is not the place to discuss whether the cerebral cortex of *homo sapiens* was developed by the dexterity and sensation of the hand or vice versa. This is a philosophic question, which emphasizes the importance of the hand. The human hand is extremely mobile, extremely sensitive in matters of touch discrimination and, in addition, has the capacity (because of the opposition of the thumb) to grip a suitable sphere (or ball). It is important that these qualities of the hand should be preserved after injury, and especially after any amputations—i.e., in the "residual" hand.

Damaged digits which will interfere permanently with the dexterity, mobility or sensation of the integral hand should be amputated early, for long persistence in some endeavor to save a doubtful digit may result in loss of function of the entire hand. Amputation stumps should be mobile and not tender, lest they interfere with the grip. Where the whole digit is lost, the index and fifth fingers should be resected obliquely through the midmetacarpal, to afford a well shaped palm in the residual metacarpal heads. The middle and ring fingers should be divided at the knuckles. Phalangeal amputations are not infrequently followed by complaints of tenderness if the expanding phalangeal articular end is left, if the scar is terminal instead of dorsal, and, in other cases, where no organic lesion exists and where most measures prove to be ineffectual.

There is a tendency to ignore the sensation of the fingertips and concentrate on mobility. Neither quality alone is responsible for the unique functions of the hand, and nerve suture and graft are necessary in the repertoire of the hand surgeon. Nevertheless, the most common cause of disability is interference with mobility. This will be conserved if all the small joints of the digits are passively or actively moved through their full range every day. Any immobilized segment of the hand must be placed in the "position of function." This has been widely described by writers on the subject, but amounts to the fact that the thumb is in line with the radius (both laterally and anteroposteriorly) with all the small joints semiflexed, and the arch of the palm conserved as though the hand lightly gripped a suitable ball. Unnecessary immobilization is, of course, much to the detriment of the entire hand and should be conscientiously avoided if mobility is to be preserved.

The ravages of infection in the hand, the tender, rigid scars which result, and the serious disabilities following edema and its resolution are much diminished if antibiotics and

immediate skin cover of bare areas are fully employed. The latter may be achieved in one of three ways: (1) by split thickness skin graft, which is particularly suited to the hand; (2) by pedicle graft, chiefly from the abdominal wall (which is necessary to cover bare tendons, joints and bones, but often leaves a fat and ungainly appearance requiring subsequent surgery), and (3) by filletting an unwanted and useless digit and using its skin as a pedicle flap to cover bare areas.

The response of the hand to intelligent application of these principles is encouraging and rewarding, for the hand pays back in results the efforts expended by surgeon and patient.

KENNETH W. STARR

PROGNOSIS IN MYOCARDIAL INFARCTION

H. I. RUSSEK and B. L. Zohman[1] have analyzed the data derived from 1,047 cases of acute myocardial infarction, confirmed with electrocardiograms, seen in three New York hospitals. The ages of the patients varied from 30 to 88 years. The anticoagulants were not used in treatment. Four hundred eighty-nine patients were classified as good risks since they had none of the following criteria of poor prognosis on the day of admission:

1. Previous myocardial infarction.
2. Intractable pain.
3. Extreme degree of persistence of shock.
4. Significant enlargement of the heart.
5. Gallop rhythm.
6. Congestive heart failure.
7. Auricular fibrillation, ventricular tachycardia or intraventricular block.
8. Diabetic acidosis, severe obesity, previous pulmonary embolism, varicosities in the legs, thrombophlebitis or other conditions encouraging thrombosis.

The authors' analysis of results showed that only 3.1 per cent of patients who had a first attack and entered the hospital with a benign picture subsequently died during hospitalization. Almost half of these few deaths occurred during the first 48 hours.

Drs. Russek and Zohman point to the critical period that prevails during the first few days of the attack, and the increased hazards resulting from physical and psychic trauma, attending needless removal to the hospital. They believe that routine administration of anticoagulants in all cases of myocardial infarction subjects the patients to an unwarranted risk. In fact they are convinced that anticoagulant therapy is likely to influence the uncomplicated first attack.

In the light of these observations a more optimistic attitude is warranted about the recovery of all "good risk" patients.

MORRIS FISHBEIN

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UNIVERSITY OF ILLINOIS STRENGTHENS RURAL MEDICAL PRACTICE

THE University of Illinois College of Medicine is accepting a maximum of 10 students each year in its incoming class as a means of aiding the settling of physicians in rural areas. The program is jointly sponsored by the Illinois State Medical Society and the Illinois Agricultural Association and has been affirmed by the University of Illinois Board of Trustees which has approved a recommendation made by a Committee on Physicians for Rural Areas. The program has been in operation tentatively since 1948.

Applicants qualified by scholarships are given entrance to the medical school but they must meet the minimum admission standards of the College of Medicine. They do not have to meet the severe premedical scholastic competition of other applicants. They enter the medical school with a loan but they are required to return to rural areas to practice and they must remain in such rural areas for at least five years after graduation and must pay back the loan at an interest of 2 per cent. With 1954 the new dentistry-medicine-pharmacy building of the College of Medicine will be completed and the entering class will be increased from 166 to 190. Obviously this

is a practical method of aid to the project of settling well trained physicians in rural areas. A young man who has worked in a community for five years is unlikely to leave unless he determines to take additional education to qualify himself for specialistic practice.

MORRIS FISHBEIN

CHANCROID

In its *Medical News Letter*, the United States Navy calls attention to the fact that the incidence of chancroid has reached such a low level within the continental United States that research on this problem has come to a virtual standstill. Investigations by the World Health Organization show, however, that throughout the Far East and elsewhere the incidence remains high or is increasing and there are still many problems concerning the epidemiology of chancroid that have not been answered. Reports in many places show that penicillin, terramycin and similar antibiotics have brought gonorrhea, syphilis and chancroid under control, but here and there other organisms related to venereal disease are beginning to have effects.

Chancroid is a disease of filth and neglect and is found usually among uncircumcised men with low standards of personal hygiene. The skin of the affected tissue usually has been broken or damaged and because of this the organisms gain access. The disease is comparatively rare in women although the woman is the only source of the male infection. Ninety-five per cent of reported cases are in men.

In early medical writings, syphilis and chancroid were often confused because both infections occurred at the same time. Now it is known that syphilis should be suspected in every chancroid which does not respond to usual treatment. In every case the serologic test for syphilis should be mandatory. Chancroid does not respond to the commonly used antisyphilitic drugs. In positive diagnosis the smear, culture and skin test may be employed. Subinoculation of exudate from a lesion into the skin of a patient, just as a smallpox vaccination is done, will produce a pustule after three or four days, from which the organism can readily be identified. The procedure also may be carried out in rabbits. Since several days' time may be required, it is done only where absolute verification is necessary before treatment is begun.

Fortunately a dosage of 4 gm. of sulfonamide drugs a day until the lesion disappears is usually successful in curing it. Streptomycin, AUREOMYCIN®, CHLOROMYCETIN® and terramycin, according to the report from the Navy, are also highly effective in total dosage of 5 to 10 gm. Since, however, all of these drugs, except streptomycin, also influence the course of any simultaneous syphilitic infection, the venereologists prefer to depend on sulfonamide drugs so as not to mask the syphilitic infection.

Ten years ago a prediction of such powerful control over venereal diseases as has now been secured would have been considered a fantastic dream. Unfortunately the vast majority of the public has not yet begun to appreciate the gain in years of freedom from illness, prolongation of life and the economic values that have been achieved by this single phase of medical progress.

MORRIS FISHBEIN

SKIN CLEANERS

The relatively recent development of knowledge about the effects of a variety of industrially used chemicals on the skin has brought skin cleaners into great prominence. Workers have known that a variety of fat and alkali compounds with added glycerin will produce soap and that soap is in general a cleaner, but that crude soap may do more harm than good. In fact, as stated in *Occupational Hazards*, "The very qualities that make a cleaner good for dirt removal can make it dangerous." Dermatologists say that 9 out of 10 cases of industrial dermatitis would not occur if workers would wash regularly each time they leave their work. However, the neglect to remove cutting oils, lubricants, solvents, paints and varnishes from the surfaces of the skin may lead to serious irritation and secondary infec-

tion. Some workers are, of course, specifically sensitive to certain irritants. The industry is further concerned that an acceptable skin cleaner must not only remove soil but also do it quickly or there develops a bottleneck in washroom traffic, a waste of cleaner and a resistance to use of the cleaner by the workers. Furthermore, the cost of purchasing cleaner and using it may be considerable.

In a complete review of the subject, *Occupational Hazards* points out that an effective skin cleaner must contain material capable of loosening and breaking up dirt film, a detergent for cleaning, a suspending medium, emollient and, occasionally, an antiseptic. Cake soaps are easiest and simplest to dispense. Liquid soaps are easy to use but must be associated with a suitable dispensing system. Granular soaps afford saving in shipping and storage but are associated with a special problem of dispensing. Waterless cleaners are useful for carrying, particularly around machinery and motor cars. When an antiseptic is needed, the one now usually used is hexachlorophene which apparently can be included in a soap without having irritant or toxic properties.

The virtues of skin cleaners are now recognized. The Committee on Cosmetics of the American Medical Association has examined many of these products and certified to their harmlessness and usefulness. Certainly they constitute a major weapon in the continuous warfare against industrial dermatitis.

MORRIS FISHBEIN

Skin cleaners: what you should know about them. Occupational Hazards, p. 45 (March) 1953.

THE GREEN WAVE OF CHLOROPHYLL EBBS

No doubt the time will be short till the green wave of chlorophyll that threatened to inundate the United States will begin to ebb. Chemists at Glasgow University have been testing chlorophyll against the smell of skunks, perspiration, chopped onions, garlic and foul gases and conclude that it has no deodorant properties whatever. This result was predicted in *Postgraduate Medicine* well over a year ago when the wave first began to rise. Dr. John C. Brocklehurst of the Department of Materia Medica at Glasgow worked out a test in which mercaptan, the foulest gas he could find, was passed through tubes of chlorophyll and then through a reagent, iodine, so that it could be found how much of the foul-smelling gas had been absorbed by the chlorophyll. Dr. Brocklehurst observed, as reported in the *British Medical Journal*, that just as much of the gas was absorbed by water as by chlorophyll. Similar tests were made with other offensive odors.

In a final test, Dr. Brocklehurst and his associates swallowed more than 25 times the number of tablets of chlorophyll recommended as an ordinary dose and found that the characteristic odor caused by asparagus in the urine was not removed, nor was there any effect on the odor of perspiration from the armpits.

The announcement from Great Britain caused consternation among the purveyors of chlorophyll as a deodorant in the credulous United States. They met in New York City, as reported by the New York *Times*, and apparently did not wish to take this announcement "lying down." Nevertheless, Dr. Sam Granick of the Rockefeller Institute for Medical Research said that the United States extractors of chlorophyll "do not have a leg to stand on" in claiming that a pill taken by mouth can deodorize. This statement was agreed to by Dr. A. H. Corwin, head of the Department of Chemistry at Johns Hopkins University. Indeed he asserted that chlorophyll masks odors because of the mixtures that are sold. Mixed with licorice the smell is like licorice and mixed with mint the smell is like mint; it is the odor of the substance added that masks the odor that is said to have disappeared because of the chlorophyll.

Apparently the only joy to be derived from the current situation is that of the growers of alfalfa who sold 40,000 tons of high grade alfalfa last year for making chlorophyll.

As one views the current situation, one is impressed by the fact that these waves of enthusiasm come oftener nowadays but they also disappear faster.

MORRIS FISHBEIN

John Arderne, The Father of English Surgery

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John Arderne, a fourteenth century Englishman, was a master of the art and science of surgery. He gained knowledge far in advance of his times through experience, common sense and available literature. His results and views he committed to writing and illustration which established surgical principles and technics that merited him the title, "Father of English Surgery."

MEDICAL science prior to the fourteenth century made little if any progress in England, nor was there before this time—with the possible exception of Roger Bacon—a single medical writer who distinguished himself in the annals of medicine and surgery in the British Isles.[1] Then, in the course of this century appeared John Arderne, later to be known as the "Father of English Surgery." Autobiographic details preserved with his manuscripts, which were written in Latin and later translated, and a small body of traditional knowledge are the only sources of information concerning him. It is because so few of these manuscripts have been printed that he has not occupied a more prominent place in the history of medicine.

John Arderne seems to have been a member of the early Saxon family of Arderne, or Arden, though to which branch he belonged is unknown. The date of his birth is clearly established as 1307 by his own statement in his manuscript, "De Cura Oculi," that this treatise was written in his own hand at London in the first year of the reign of King Richard II and in the seventieth year of his life.

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Early Training and Practice

Of his early professional training as a surgeon little is known. According to the British Dictionary of National Biography,[2] ". . . the first Englishman who displayed much skill in surgery was a layman, not a doctor of medicine, and practiced in the time of Edward III." It has, however, been asserted by many authors[3-7] that he was admitted to the University of Montpellier and that he practiced in France as a military surgeon. If this is true, Arderne attended the finest medical school of his time. Montpellier, situated in southern France, was in touch with Arabic learning and was liberal enough in the early fourteenth century to sanction cultivation of anatomic and surgical science in extramural classes in which, among others, Guy de Chauliac, the greatest surgical figure of the age, took a part. Though there is historical doubt as to his academic medical training, John

FIGURE 1. Facsimile of part of a Latin manuscript by John Arderne in the Surgeon General's Library, Washington, D. C. Showing top half of page (slightly reduced). (Pennington.[17])

Arderne was by his own statement a "Chirugus inter Medicos"—a surgeon among physicians. His manuscripts attest to a fairly good education, for they are written in passable Latin; he quotes freely from the Arabic and Greek, and shows evidence of having been well read in the available literature of his profession. In regard to practical surgical training, he spent many years in France with an adventurous career as an Army surgeon.[8-13]

Arderne obviously practiced abroad, for in his own manuscript one will find the statement that he tried a remedy "in foreign parts upon one King and two Bishops."[14] No doubt the King referred to was John of Gaunt, also known as the King of Castile, at this time (1376) the most hated man in Europe. Arderne's omission of his name was wise; only five years later a London mob burned Gaunt's palace and killed his personal physician merely because he was a trusted and valued friend. In his manuscripts Arderne reveals not only his familiarity with war wounds but also his intimate knowledge of several campaigns of the Hundred Years' War. If we agree with the statement of Hippocrates, "War is the only proper school of the surgeon," then there is little doubt that Arderne was well grounded in the art and science of surgery. From his writings it can be deduced that he probably was a surgeon in the military service of Henry Plantagenet, the first Duke of Lancaster, and that in this capacity he visited Antwerp in 1338, and Algeciras, where gunpowder is said to have been employed for the first time, in 1343. He was also present at Bergerac in 1345, and at the Battle of Crécy in the year 1346.

After this historic battle, John Arderne, at the age of 40, returned to England a successful surgeon with many influential friends. He married and settled with Ellen his wife at an estate in Mitcham in Surrey, but within a year his wife had died of the Black Death. His place of residence after this tragedy is recorded in an autobiographic notation which reads, "I, John Arderne, from the first pestilence that was in the Year of Our Lord 1349 dwelled in Newark in Notinghamshire unto the Year of Our Lord 1370."[14] In one manuscript is a record of his generous practice in Newark, where he describes treating noblemen, knights, priests, merchants, friars and the needy. During his 31 years there, he established a large surgical practice and when, in 1370, he went to London, he continued professional practice for another six years with remarkable vigor and success. Subsequently he issued the best known of his treatises on fistula-in-ano, with the prefatory remark that it was "written with my own hand in the year when the strong and war-like Lord (Edward the Black Prince) was taken to God."[14] This event (the death of Edward III) took place in 1376.

FIGURE 2. A Master of Surgery (John Arderne) in the act of operating on a fistula-in-ano. (From Editorial of Brit. J. Surg.[10])

There is no evidence that Arderne was living when Henry IV came to the throne in 1399, though a note of dubious authenticity in his treatise on fistula reads, "With this medicine was King Henry of England cured of the going out of the lure"[14] (i.e., sloughing of the rectum). It is usually assumed that Arderne lived until the latter part of the fourteenth century, probably dying between 1380 and 1390.

Arderne Manuscripts

Of the 60 manuscripts of Arderne's works now in existence, 22 are in the British Museum in the original Latin or in early English translations. Other manuscripts are in Oxford, Cambridge and Glasgow.[14] There is a Latin version in Stockholm, and a French version in Paris. In our own country, a Latin manuscript volume of the "Works of Arderne" was acquired in 1894 by the Surgeon General's Office. This work, as well as those in the British Museum, is considered "invariably imperfect."[6] Throughout these past six centuries Arderne's works have been referred to many times, yet only within this century has Sir D'Arcy Power presented two full and extensive texts containing translations of the master's work. Power first edited a book in 1910 entitled "Treatises of Fistula in Ano, Hemorrhoids and Clysters by John Arderne from an Early Fifteenth Century Manuscript Translation."[14] The second publication, in 1922, was a translation from a copy of the Stockholm manuscript entitled "De Arte Phisicali et de Cirurgia of Master John Arderne, Surgeon of Newark, dated 1412."[15] Aside from several commentaries[4, 16] by Englishmen who have read Arderne's manuscripts, John Reed in 1588 presented a translation of the essay on "Fistula-in-Ano," and in 1886 there appeared in South's "Craft of Surgery" a translation of Arderne's treatise "Of the Manner of the Leech."[14] The most recent reference to the technical value of Master John Arderne's works is by J. R. Pennington[17] in 1923.

In his text entitled "A Treatise on the Diseases and Injuries of the Rectum, Anus and Pelvic Colon," Pennington speaks of the history of proctology with reference to its historical-surgical aspect and refers to Arderne as being a surgeon much in advance of his time—for today the principle of his therapy for fistula-in-ano is still used. The book includes an illustration of a part of the Latin manuscript of Arderne, now at the Surgeon General's Library (Figure 1). Pennington states that the surgeon's work is original, complete and detailed, combining well both theory and practice. Riesman[18] has referred to Arderne as the "first proctologist." It is likely that much of Arderne's experience was acquired in France, for the rigors of war of that day contributed greatly to the development of ischiorectal abscess and subsequent fistulas. When he later returned to Newark, he developed an extensive practice involving the treatment of this malady. Prior to this time fistula-in-ano was considered incurable and inoperable. The only contemporary known to Arderne to have attempted its surgical treatment was an insignificant retainer of the Black Prince, whom the master classed as a fraud.

A frequently reproduced picture of Arderne

(Figure 2) is one in which he is probing a fistula-in-ano—with the patient discreetly omitted. The original picture from Arderne's manuscript is more revealing, showing both the surgeon and the patient. In both versions of the print, Master John Arderne is seen in the Long Robe of his profession, which distinguished him from the Barber Surgeons of the time who wore the Short Robe. Membership in the Guild of Surgeons of London gave one the right to prefix "de" to his surname, and in that manner was derived his title, Magister Johannes de Arderne.

Operative Technic for Fistula-in-ano

In writing of the treatment of fistula-in-ano, Arderne[14] considered the influence of the moon when choosing the day for the operation, in accordance with the practice of his time. On the other hand, he advised preoperative selection of patients whose skin is "well colored" and who are "good hearted and abiding."

They should be taken "to a place made ready," that is, an operating room, where there must be good light upon the operative field. The patient should be placed in a lithotomy position and the surgeon should have an assistant. The patient is advised before the operation to be brave and obedient.

The technic described by Master Arderne is said to resemble somewhat that recommended by the Arabian physician Albucasis in the tenth century. The finger is lubricated and placed into the rectum to determine operability, for if a cancer were found the operation would not be undertaken. A probe *(sequere me)* is inserted into the fistula and through its eye four strands of ligature *(Fraenum Caersaris)* are passed. It is removed by way of the rectum, leaving the ligatures pulled through the fistula. The two ends are knotted together and the entire ligature tightened. A dilator *(tendiculum)* is then inserted into the fistula and by means of a peg *(vertile)* fixed to the widest part of the dilator the ligature is tightened in the way that a violin peg tightens a string about it. A grooved director or snouted needle *(acus rostrata)* is passed along the fistula until it projects into the rectum and a shield or spoon *(cochlearia)* with a depression at its center is passed through the anus until the grooved director engages in the depressed notch. The spoon protects the surgeon's own finger and also the wall of the rectum, particularly should the patient move. A lancet is passed along the groove in the director and the fistula is divided along its entire length by drawing the knife, dilator, grooved director and spoon out of the rectum with one single movement, the ligature coming away at the same time. Arderne specified that each branch of the fistula must be laid open in the fashion just described. Bleeding is stopped by a sponge with pressure and the wound dressed clean with styptic powders. A T-bandage is the best to apply following the operation.

Postoperatively, the Master Surgeon relates that the patient's bowels should not be moved for 48 hours following the operation and, after a movement, the area should be thoroughly cleansed and dried. After the blood has clotted well, two or three days postoperatively, soothing ointments might be applied. Clysters or enemas are suggested for nine consecutive days. By the twenty-fourth to twenty-sixth day healing should be near completion. It is only after this that caustics may be applied.

The surgeon concludes with the statement that the best sign of a cure is that the dressings are dry. In spite of the rather unnecessarily complicated surgical technic for the treatment of this condition, Arderne was the first Englishman to advocate a principle of treatment for fistula-in-ano that is used in part even today, the so-called "laying open" of the fistulous tract.

"Bubo Within Lure"

Power's translation of Arderne's "Treatises of Fistula in Ano, Hemorrhoids and Clysters" deals not only with the subjects indicated in the title but also with cancer of the rectum, fistula of the extremities, ulcers of the leg, tenesmus, rectal prolapse, powders, oils and waters, and valences. Arderne's description of, and advice concerning, rectal carcinoma ("bubo within the lure") are classic and still valid. I venture to suggest that this short treatise found in the fifteenth century manuscript should be a reading requisite for all medical students and physicians.

Arderne described a bubo as a "tumor within the rectum which is of great hardness, but little aching. It is called 'bubo' because as Bubo, an

owl, it dwells best in dark places and so this sickness lurks within the rectum in the beginning, but after a period of time it ulcerates and sloughs out." Oftentimes it causes incontinence. The diagnosis is made by inserting the finger into the rectum and if within it is felt a hard thing, as a stone, sometimes on one side, sometimes on both, which prevents defecation, it is a bubo. The signs of ulceration are pain, aching and sharp, that drives the patient to relieve himself two and three times every hour and the stools are streaked with watery blood and are foul-smelling. To well meaning though unknowing doctors, as to the patient, this appears to be dysentery. Dysentery, however, is a diarrhea, but bubo produces hard stools which cannot at times go past the obstruction and must be removed with the finger. Unsuspecting leeches administered drugs to stop the dysentery, but Arderne gave medicines in which experience had given him confidence. He used a simple enema of bran water or mallows, without oil, butter or other fats, since fatty substances, he thought, nourish the cancer and feed it.

The symptoms of those who have bubo in the lure are not unusual at first for they are as normal individuals. Toward the end, they lose their appetite and eat less meat, which does not, however, absent them from the toilet. The patients often die in the autumn and near the end run a low grade fever, having lost their appetite to the extent that they crave only ale or wine. Finally, day by day, they grow more feeble until they become bedridden and take little water. Death is then at the gates; nevertheless, they may speak, raise themselves up and move about to the very end. Simple clysters relieve the patient greatly. Care should be taken in these cases to use palliation and the friends should be warned of the incurability of the disease. Such prognostication will allow for more respect for the profession of the leech; therefore, one should avoid misdiagnosis and abstain from false treatments.

Arderne also stresses the importance of a rectal examination in a patient with dysentery. Summarizing the differential diagnostic features of the two conditions, he notes that the pain of dysentery is in the navel or flanks, whereas a bubo is characterized by an aching, sharp, stirring pain, with a desire to defecate, and tenesmus. In conclusion, Arderne points out that such cases are to be treated advisedly so that blame will not be brought forth upon the leech, for, he adds, he has never seen nor heard of any man cured of the bubo, but he has known many who died of it. It is amazing to observe the amount of knowledge possessed by this Englishman of 600 years ago; some physicians do not appear to possess it even today.

Other Arderne Treatments

Master Arderne next presents his treatment of pruritis ani and fistulas of the fingers, legs and joints—all apparently personal observations that owe nothing to tradition. In treating an inflamed sore of the leg he advised bandaging and the use of hot and cold compresses and later mercurial ointment. Should dead flesh appear, he suggests debridement be undertaken ("it is profitable to cut the dead flesh and put it away if the patient consents").

In the essay on hemorrhoids Arderne, for the first time, appears as a compiler, conscientiously avowing his indebtedness to the older masters of his craft, whose doctrines he accepted and upheld. This discussion is somewhat obscured by the nebulous theories of his predecessors in contrast to his own practical and original writings. His own treatment, on the whole, is fairly sound, although he was unable to shake off some of the ancient superstitions shared alike by the wise and the foolish; for example, operations about the anus could be performed only at certain times of the year, hemorrhoids and menstruation were believed to be provoked by phlebotomy of the internal saphenous vein, while blood-letting from the external saphenous had a directly opposite effect.

It appears that other features which currently we would call the nonoperative treatment of hemorrhoids differ but little from those recommended by Arderne. Styptics and soothing ointments were applied to the pile, the cautery was used to stop the bleeding, soothing compresses were used in inflamed cases, while thrombosed hemorrhoids were incised and evacuated. This latter treatment, he advised, should be kept secret lest the Barbers learn of this simple cure, to the detriment of the Master Surgeons. Clys-

ters, too, were used as soon as the improved hemorrhoidal condition permitted.

In a treatise on clysters, the author finds himself once more on the safe foundation of extensive experience. He relates the details of preparing an enema and advises the use of a simple solution, the simpler the better. The use of clysters for the diagnosis of worms is of as great value as are the signs of blood or pus in the stool following evacuation. The administration of an enema is advised in colic and "yliac passions" and may even be given seasonally to prevent illness. The use of a nutrient enema is advised for patients destitute of appetite.

Drug Preparations in Surgery

The final section of this manuscript is devoted to drug preparations used in surgery. It is particularly interesting because it is full of the superstitions of Arderne's period. In spite of the confusing array of pharmaceuticals, the surgeon attempted to use them with judgment. With his characteristic honesty, he confessed his mistakes. Particular reference can be made to his youthful experience with arsenic, when he almost killed two patients while attempting to use it as a local application. As it happened, the patients survived, although each developed subsequent necrosis of the tibia. He opposed meddlesome surgery. He advised against caustics, preferred bland soothing concoctions, would dress wounds daily or every third day, and remarked on the value of sleep to the sick man. Of course, the preparations employed reflected the mysticism with which the use of drugs was then surrounded. One preparation called "sanguis veneris" and composed of aloes, myrrh, other drugs and blood was used for application to ulcers and to wounds. The valued ingredient, blood, had to be that "of a maiden virgin or of a maiden damosel about 19 or 20 years who was never impregnated though she be corrupt," for, adds our observant and diplomatic author, "virgins cometh now full seldom to 20 years."

Having summarized briefly Power's translation of Arderne's "Treatises of Fistula in Ano, Hemorrhoids and Clysters," let us consider the latest translation of the Latin Stockholm manuscript (Figure 3), "The Practice of Master John Arderne of Newark in the Art of Medicine and Surgery, 1412,"[15] which was probably sent to a grandniece of John of Gaunt, who had married the King of United Norway and Sweden in 1406 and had gone to live in Stockholm. The diseases discussed (Figure 3) include wounds, "yliac passions," rectal prolapse, intestinal parasites, gonorrhea and urethral stones. Therapy is even recommended for the cough of a cold and simple remedies are offered for hiccough. The termination of the manuscript concerns care of obstetric cases.

It appears from this manner of presentation that there existed no method or organization in Arderne's writing. He issued his writings in the form of treatises which were collected after death, recopied, and translated at various times during the fifteenth century. These treatises actually constitute a "System of Surgery" which, compiled, form one of the epoch-making books in British Surgery.[20] The material here presented forms a large section of the System but there are also divisions on Hemorrhage (describing the manner in which patients should be bled and how bleeding can be stopped), Diseases of the Eyes, Diseases of the Male Generative Organs and the Kidney, and Diseases of Women. There exists a supplementary section in which is described a series of interesting cases which had come under his care.

Arderne Contributions

Arderne's real fame lies in his contribution to the art and science of surgery.[21] He established in his writings rules of etiquette for the surgeon of his day and the centuries to follow. In his treatise entitled "Of the Manner of the Leech," the Master Surgeon attempted to elevate the position of surgery, as it was known then, by inculcating into the neophyte surgeon honesty, frankness, humility, kindness, poise, professional courtesy and confidence, and a wholesome appearance supported by wordly wisdom. This wisdom was to be based upon knowledge, which in turn was based upon experience. Quoting little, yet maintaining a familiarity with the medical works of his time, Arderne's works were singular in an age when most medical writers were nothing more than mere copyists. Of his surgical writings, it has been said, "His descriptions are clear and con-

FIGURE 3. A portion of the Stockholm manuscript by Arderne, written on vellum and containing two columns of Latin script. The illustrations are related to the diseases and procedures under discussion. In the left-hand column are illustrations dealing with epilepsy, early leprosy, deafness and acne. In the center a fistula-in-ano is being probed, and there are illustrations of a sagittal section of the human body and of syringes for irrigations and enemas. In the right-hand column one sees a gouty hand, a patient with spasm (that is, cramps), one with bleeding hemorrhoids and one with inflamed hemorrhoids. (From Power.[35])

cise; his remarks practical and full of common sense; in short, he anticipates in a startling manner those qualities which have been known in later times as characteristic of the English School of Surgery."[2]

An outstanding innovation of Master John Arderne was the illustration of pathology and of the instruments he used. For the first time in English surgery there was an endeavor to convey to the reader ideas of living pathology by means of visual impression.[5] This is the pedagogic principle at the basis of modern medical education. Furthermore, a compilation of series of cases with a statement of results, the very basis upon which current journals are published, can be traced back to Arderne's manuscripts, in which patients are identified by their armorial bearings.

The technical value of the medical and surgical knowledge produced by Arderne can be judged by the extracts from his works already presented. Short, accurate and concise descriptions of such things as tetanus, carcinoma of the male breast, gonorrhea and its treatment by irrigations, and excision of urethral stones make interesting reading and no doubt contributed to early recognition and understanding of these surgical diseases. The lesson the Master Surgeon learned centuries ago, not to confuse dysentery and other rectal diseases with "bubo in the lure," is today incorporated in axiomatic teachings of the proctologist. The earliest understanding of surgical treatment of fistula-in-ano we owe to John Arderne. It is unfortunate that English surgeons did not adhere to Arderne's teachings of healing without suppuration, avoidance of irritating applications and infrequent dressings of the wound to permit healing. It is also unfortunate that his erroneous pharmaceutical knowledge for centuries overshadowed his outstanding surgical contributions. Three of the preparations he concocted appeared in the first British Pharmacopoeia of 1618 and some of them were in use as late as the eighteenth century.

From the evidence presented here, we can better understand why John Arderne has been called the "father of English surgery." William Black[22] in 1782 wrote a book which bore the pretentious title of "An Historical Sketch of Medicine and Surgery from Their Origins to the Present Time and of the Principal Authors, Discoveries, Improvements, Imperfections and Errors." In the chronologic chart of medical and surgical authors the first English surgeon listed was John Arderne, who appeared in the fourteenth century with Guy de Chauliac, the father of French surgery, as his sole contemporary. William Anderson,[16] a Fellow of the Royal College of Surgeons, who recognized the importance of the contributions of Arderne, said that "a dozen men of the stamp of Arderne would have changed the whole history of Eng-

lish surgery." In a paper delivered in 1897 before the Medical Society of London he so skillfully evaluated the importance of John Arderne that his appraisal forms an applicable conclusion to this study:

> "It is difficult at the present time to adjudge John Arderne's claim upon posterity, but when we remember into what low repute the art of surgery had fallen in his day in England, and how honestly and successfully he strove to elevate it by his example and teachings, we can scarcely do him too much honor. His art was not all we now understand as surgery, although he at least revived two of the ancient operations of the Greeks [operation for fistula in ano and urethrotomy for urethral calculi], but he was a true clinical observer and based his treatment on experience and reason rather than on precedent and superstition. He was, moreover, almost the only English surgeon of his century who is known to have combined the actual practice of his calling with a scholastic training sufficient to master the surgical literature then available and to commit his views and results clearly to writing . . .
>
> "Of the man himself his book conveys a vivid picture. It is easy to see him as the leech of courtly and obliging manners, sober in attire and moderate in speech, and endowed with a self-restraint born of self-respect, with a tact that bore him well through the many difficulties that must have beset the thorny path of the chirurgeon in his day, and with a strong common sense that never rose too near to the dangerous level of genius; a good man and true, kindly and honest, but shrewd withal, with a quick eye to the main chance and a capacity for raising expediency to the dignity of principle. He was through all a surgeon, a scholar, and a gentleman, and in the records that he bequeathed he stands before us as one whom we, his professional descendants, may accept with pride and veneration as the Father of English Surgery."

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Letters from Abroad

FROM POSTGRADUATE MEDICINE'S CORRESPONDENTS

AMSTERDAM

Minister for Economic Affairs fixes specialists' fees—The Dutch medical world has been disturbed by a price regulation for specialized medical treatment of members of a "Ziekenfonds" (Regional Health Insurance Company), which became effective January 31, 1953.

In the Netherlands the larger part of the population must be insured with a regional health insurance company against illness (hospital charges, doctor's fees, etc.). The insurance of persons with an income lower than a fixed amount is compulsory while for those with a higher income, voluntary insurance is available.

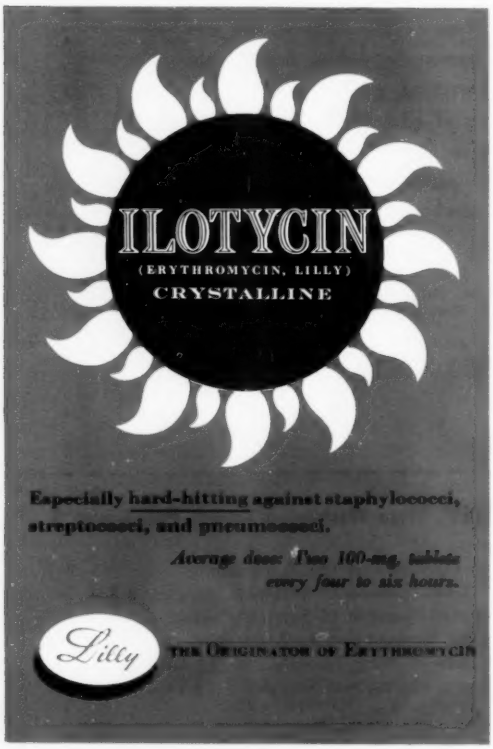
In 1949 an agreement was reached between the National Association of Specialists—of which every specialist was then a member—and the joint regional health insurance companies whereby specialists' fees for treatment of health insurance patients were fixed equally for the whole country. As most of the population is thus insured, the income of most specialists derived from health insurance practice is considerably higher than from their private practice.

Owing to the financial difficulties of the regional health insurance companies, the 1949 agreement was revised in 1952. In the 1949 agreement a progressive deduction on higher incomes of specialists derived from the health insurance practice was added. In 1952 changes in the progressive deduction were made and simultaneously a maximum amount was fixed for the total cost of specialized treatment, with the understanding that should this maximum be exceeded, the risk would have to be divided equally between the specialists and the health insurance companies.

Although the National Association of Specialists objected to this maximum, they accepted the agreement for one year because of the financial difficulties of the health insurance companies. However, a number of specialists (over 200) disagreed with the new plan to such an extent that they resigned from the National Association of Specialists and started a new association.

Negotiations between this new association and the health insurance companies were without result and from January 1, 1953 these specialists

(Continued on page A-14)



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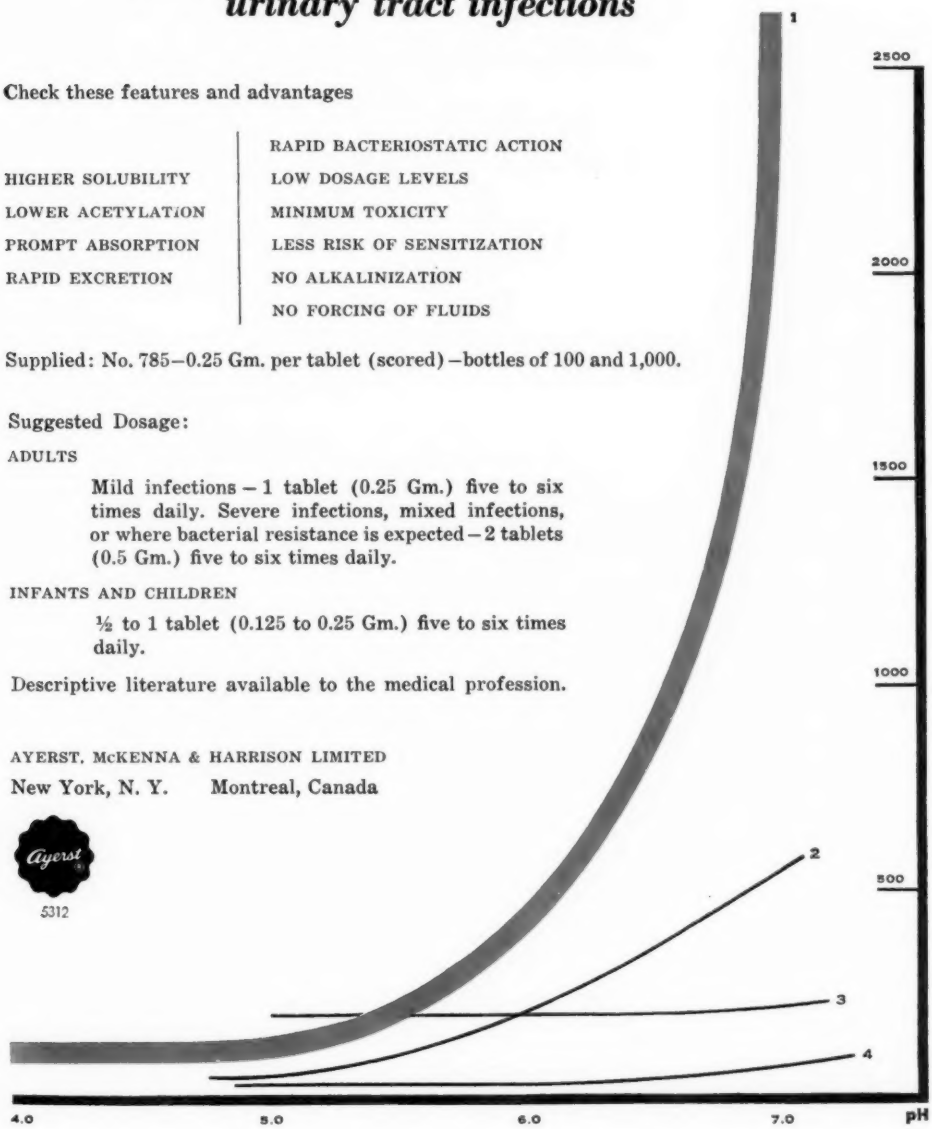

charged the fixed fees but without deduction. In this way the charges for specialized treatment to health insurance patients became approximately 16 per cent higher.

The Minister for Economic Affairs did not accept this 16 per cent increase in fees. According to a law on raising prices he was entitled to issue the price regulation which came into force on January 31, 1953. This regulation fixes the maximum fees specialists may charge for treating health insurance patients, but does not apply to the treatment of private patients, nor to the fees of those specialists who had accepted the 1952 agreement with the regional health insurance companies.

The government has expressed the hope that negotiations will be resumed and that a solution will be reached which will make the price regulation superfluous. However, in the Dutch medical world this interference of the government is on the whole considered a dangerous precedent of which the significance cannot yet be calculated.

International congresses—The fifth international Congress for Otology, Rhinology, Laryngology, Bronchology and Esophagology will be held in Amsterdam June 8 to 13, under the presidency of Dr. Eelco Huizinga, professor at the University of Groningen. This congress will be preceded on June 6 and 7 by the third Congress of the Association Internationale pour l'Etude des Bronches, to be held at Utrecht under the presidency of Dr. Bronkhorst, professor at the University of Utrecht. The seventh annual Assembly of the World Medical Association will meet in the Netherlands in 1953 under the presidency of Dr. L. A. Hulst.

The Medical Muse

RICHARD ARMOUR

MEMORY AID

"Doctor," she says, "I have written a list
Of my symptoms, for fear I'd forget them.
They're here in my bag, if I only can find
The paper on which I have set them.

"Yes, here they are, doctor; I have here the list
Of the things that I've carefully noted:
A pain that begins in the small of my back
And my being so terribly bloated.

"And a dozen loin chops and it hurts me to breathe
And a couple of pounds of tomatoes
And a rash on my chest and a small piece of cheese
And chills and a sack of potatoes."

BEDSIDE MANNERS

The bedside manner's of many a sort:
There's the tersely professional, busy and short.
There's the calmingly competent, leave-it-to-me kind,
As well as the studious, now-let-me-see kind.
There's the jovial type, with a hearty guffaw
And a head full of jokes, about half of them raw,
There's the chucking of chins kind, and holding of hands,
That the woman who's fiftyish all but demands . . .
Though manners may vary in type and condition,
There's one that's the same for each normal physician,
Yes, one bedside manner is constant and deep:
When the bedside is yours, and you're half-dead for sleep.

sombulex* *is an unusual barbiturate*

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Your Questions answered

Readers may send questions from their own practice or other medical problems which will be answered by qualified consultants.

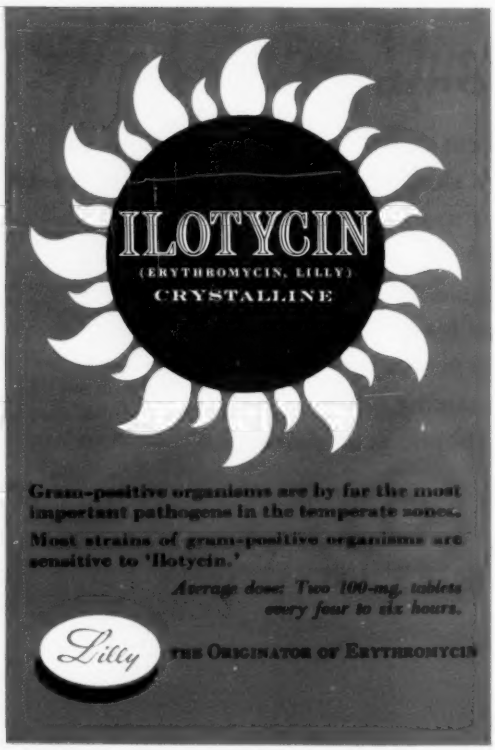
• ELECTROLYSIS

Question: Can the removal of unwanted hair be done safely? What equipment is required?

M.D.—Michigan

ANSWER: Unwanted hair can be removed successfully by electrolysis if done by a capable technician. If not properly applied, the procedure can be followed by marked scarring. The required equipment is a source of galvanic current, fine needles for introduction into the hair follicles, and other accessories. This equipment can be purchased from any medical supply house.

BEDFORD SHELMIRE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• REMEDIES FOR MOTION SICKNESS

Question: Since the discovery of DRAMAMINE®, experimentation on motion sickness has been reported from various portions of the world with the old-fashioned drug containing hyoscine and also with some of the newer antihistaminics, the barbiturates and physical methods. What is the present status of the use of these remedies; is any one of them so outstanding as to be preferred over the others?

M.D.—Ontario

ANSWER: The present concept is that dramamine, products containing hyoscine, BENADRYL®, PYRIBENZAMINE® and the short-acting barbiturates such as SECONAL SODIUM® have about the same order of effectiveness in preventing the development of "motion sickness." There are certain individuals who will be protected against motion sickness by any of these products; at the other extreme, some individuals are not protected by any of them. Not one of them has proved to be definitely superior, as I understand it.

JAMES C. MUNCH

• VIRAL HEPATITIS

Question: An acute ailment, which I am diagnosing as "viral hepatitis," is now prevalent in this community in endemic form.

Jaundice is not marked—the skin almost not jaundiced at all, the sclera only slightly so—but the urine contains much bile early and has a characteristic "jaundiced" color. Vomiting is usually present, as is hepatic enlargement and tenderness. The spleen is not usually palpably enlarged. Malaise is a prominent feature. It chiefly affects school age children and some adults.

1. I know of no specific laboratory test to aid in the diagnosis. Is there such a test?
2. How efficacious is immune serum globulin

(Continued on page A-30)

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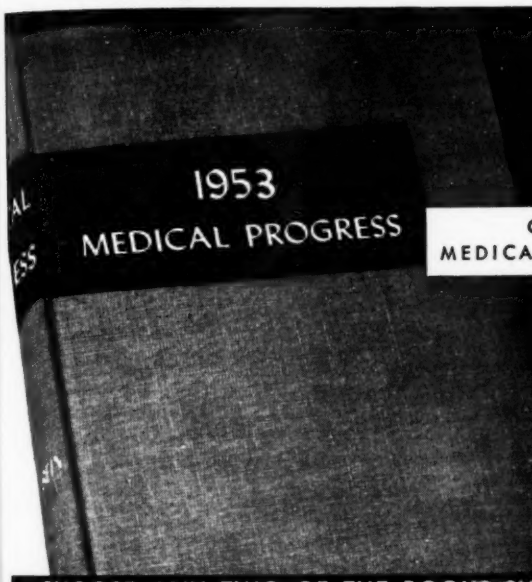

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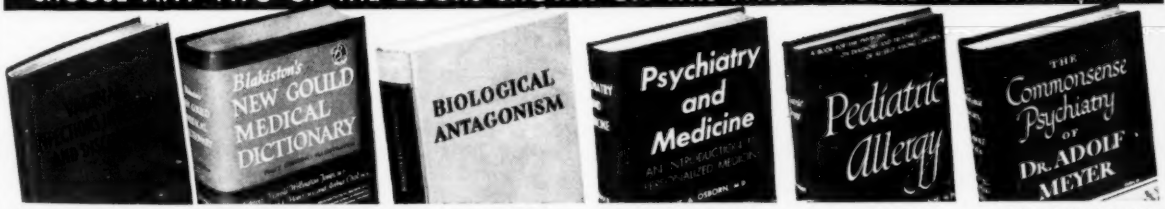

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as an agent for passive immunity? How long would such an immunity persist? What are the contraindications, if any, to the gamma globulin? Is a dosage, for this purpose, of 0.06 cc. per pound of body weight the correct dosage?

3. If less than the abovementioned dosage were utilized, is it not quite possible that the endemic would be fostered since there would be children in school who might be otherwise isolated?

4. Would the gamma globulin not be better utilized to modify an attack after the illness begins instead of administered as an immunizing agent?

5. Is it not possible to produce an heterologous jaundice by the administration of the gamma globulins?

6. What about the advisability of giving 2 cc. gamma globulin to every individual in an endemic area?

7. What are the aftereffects, if any, of this disease in children? In adults?

8. What other therapy is indicated?

9. How long should bed rest be enforced?

10. What follow-up treatment should be instituted, e.g., should the BROMSULPHALEIN® test be back to normal? Sedimentation rate? Hemoglobin and red blood cell count?

M.D.—Missouri

ANSWER: The questions are multiple, and would require much space for an adequate answer. The questions might be answered by study of the papers in the following references:

1. NEEFE, J. R.: Viral hepatitis: problems and progress Ann. Int. Med. 31:857-870 (November) 1949.
2. SBOROV, V. M. and KELLER, T. C.: The diagnosis of hepatitis. Gastroenterology 19:424-439 (November) 1951.
3. STOKES, JOSEPH, JR., BLANCHARD, MERCER, NEEFE. J. R., GELLIS, S. S. and WADE, G. R.: Methods of protection against homologous serum hepatitis. I. Studies on the protective value of gamma globulin in homologous serum hepatitis SH virus. J.A.M.A. 138:336-341 (October 2) 1948.
4. CAPPS, R. B., BENNETT, A. M. and STOKES, JOSEPH, JR.: Endemic infectious hepatitis in an infants' orphanage. I. Epidemiologic studies in student nurses. Arch. Int. Med. 89:6-23 (January) 1952.
5. POST, JOSEPH, GELLIS, SIDNEY and LINDENAUER, H. J.: Studies on the sequelae of acute infectious hepatitis. Ann. Int. Med. 33:1378-1397 (December) 1950.
6. SWIFT, W. E., JR., GARDNER, H. T., MOORE, D. J., STREITFELD, F. H. and HAVENS, W. P., JR.: Clinical course of viral hepatitis and the effect of exercise during convalescence. Am. J. Med. 8:614-622 (May) 1950.

• BLOOD DONORS

Question: What are the present requirements of the American Red Cross or hospital blood banks for blood specimens taken from donors? Are any attempts made to detect the presence of the viruses, such as that of infectious hepatitis? How thorough a case history is taken from the donor? Are examinations made with the x-ray for tuberculosis?

M.D.—Minnesota

ANSWER: Standards which have been established by the National Institutes of Health, the American Red Cross, state Departments of Public Health and accepted medical practice for blood specimens taken from donors are too numerous and too lengthy to mention as a brief answer. It is suggested that inquiry be made directly to the local blood bank now operating in the state in which the physician is practicing.

Briefly, requirements include consideration of the age, marital and military status of the individuals as well as that the hemoglobin shall be of at least a certain measure, that the temperature and pulse shall be within certain limits, that the age shall be within certain limits and that the individual does not have a history of certain diseases such as rheumatic diseases, acute respiratory diseases, diabetes, yellow fever, malaria, infectious mononucleosis, syphilis, infectious hepatitis and so on. As a rule blood is not accepted in the first six months post partum.

In answer to the second question attempts are not made to detect the presence of virus such as infectious hepatitis virus in the blood of donors. A skin test has been proposed for hepatitis virus and at present is being worked on by the National Research Council and the National Institutes of Health but so far it is not considered practicable.

Examinations with x-ray for tuberculosis are not made. However, a careful history of tuberculosis is taken. If there is any evidence of the disease in active form the donor is refused.

"How thorough a case history is taken from the donor?" A rather extensive history from the donor is taken in an effort to bring to light the presence of diseases which might in some way be important to the donor or to the recipient of the blood.

DWIGHT L. WILBUR

Which aged patient has PA...?

Pernicious anemia is basically a disease of older people. Although none of the aged patients depicted here may have pernicious anemia, it is very likely that all of them have deficient secretion of intrinsic factor, which in extreme cases would result in pernicious anemia. Among the many functions of the human organism which slow down as we advance in age is the stomach's secretion of intrinsic factor. Assure a full quota of intrinsic factor and its essential partner, vitamin B_{12}, for your aged patients by prescribing Bifacton. Only two tiny Bifacton tablets constitute a full U.S.P. anti-anemia unit, sufficient for maximal daily replacement of intrinsic factor and vitamin B_{12}.

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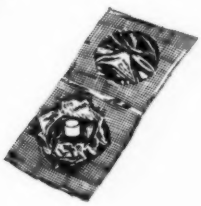

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Portraits and Personalities

EDWARD J. McCORMICK, M.D.

(A.M.A. PRESIDENT-ELECT)

A YOUNG Toledo lawyer once tried to impugn the credibility of his fellow townsman, Dr. Edward J. McCormick, as a medical expert. During a trial he challenged the doctor's qualifications on grounds that he spent more time in civic and fraternal activities than in the pursuit of his profession.

"Thanks to your dear, late lamented father," the witness replied, "I was given the opportunity to aid suffering humanity in many other ways besides the mere practice of medicine. It was he who sponsored my membership in the Elks and so gave me the chance to participate in their many good works."

After losing the case, the young lawyer confided to the counsel who had summoned Dr. McCormick as an expert witness that he would have given anything to withdraw the question.

The president-elect of the American Medical Association has for years astonished his family, his friends and his colleagues with his versatility, his diversity of interests and his great capacity for work. In his 61 years he has been unable to do just two things—to say "no" to those who would enlist his services for worthy causes, and improve a very erratic golf score. The latter project he has abandoned entirely.

When the Benevolent and Protective Order of Elks launched their cerebral palsy campaign in Ohio, Dr. McCormick became one of the prime movers in the project. Because of his unselfish devotion to the campaign, he was named honorary president of the cerebral palsy treatment center at Canton, Ohio. When the citizens of Toledo set out to establish a city manager form of government, he became president of the Toledo City Manager League in 1935. He has also found time to take part in Toledo Boy Scout activities, representing his area on the National Council; to head that city's Lions Club, and serve as trustee for the local chapter of the American Red Cross.

In 1938, as Grand Exalted Ruler of the Elks, Dr. McCormick became a figure of national prominence. Today his friends and acquaintances are as diverse as his interests and as widely scattered as his travels.

Lest the impression be made here that Dr. McCormick has been quiescent in the medical profession, "let's look at the record."

Aside from maintaining active membership in a long list of professional societies, he has over the years kept up with a rigorous surgical schedule and maintained a reputation of exceptional skill in this field. He has written and had published many articles on intestinal obstruction and general surgical subjects.

Dr. McCormick is chairman of the advisory board for Toledo's St. Vincent's Hospital, where he has been a staff member since 1922 and served as chief of staff from 1939 to 1949. He is also a past director of surgery and a trustee of the Maumee Valley Hospital in Toledo, and surgeon to St. Anthony's Orphanage. From 1940 to 1943 he served as the first president of Toledo's Board of Health. Since 1949 he has been surgeon for the Nickel Plate Railway Co.

In 1949, he was a member of the medical mission invited by General Douglas MacArthur to make a survey of Japan's health needs, and the following year he went to Geneva, Switzerland, as a United States delegate to the U.N.'s Third World Health Organization Assembly.

An advocate of physician participation in local medical societies, the American Medical Association's president-elect was for many years extremely active in the affairs of the Academy of Medicine of Toledo and Lucas County. He served as that organization's president in 1926 and on its board of trustees from 1926 to 1931. He is also a past president of the Ohio State Medical Association.

In the past decade, Dr. McCormick has con-

(Continued on page A-38)

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centrated most of his organizational activities in the American Medical Association. For two years—1943 and 1944—he was a member of the AMA's House of Delegates. When the Council on Medical Services was formed in 1943, he was appointed a member and served on that body to 1947, the last two years as chairman. In 1947 he was elected to the Board of Trustees, named a member of the Committee on Scientific Exhibit (chairman in 1950) and appointed to the Council on Industrial Health. At the 101st annual convention in Chicago last June, he was chosen president-elect.

When asked how he finds time to do all of the things he does, Dr. McCormick likes to say that he has never taken a vacation nor gone fishing. However, friends say that he has an enviable knack for finding relaxation in the company of colleagues or brother Elks during his frequent out-of-town trips. His wife, the former Josephine Beck, who used to teach grade school in Toledo and supervised the upbringing of their three sons and three daughters, says the doctor gets much enjoyment out of watching the fights on television when he has nothing else to do. "As a result of trying to keep him company on those rare occasions," she explains, "I have learned that there is some art in the so-called manly art of self-defense."

A fancier of ties and avid bedtime reader of detective mysteries (Gardner not Spillane), Dr. McCormick will drop these interests any time to see a football, baseball or basketball game. His interest in these sports dates back to his school days when he excelled in all three.

Perhaps Dr. McCormick inherited his ability to absorb a wide variety of interests from his father, the late Michael J. McCormick. In Alger, Michigan, where the AMA's president-elect was born, the elder McCormick operated a general store. Later he moved his family to Bradner, Ohio, where he leased some land and drilled for oil with moderate success. Dr. McCormick's mother, the former Mary Ellen Daily, who still will board a plane for a trip on the slightest pretext, recalls that the next move was to Toledo, where her husband bought and operated the old Grand Hotel shortly after the turn of the century. Then the elder McCormick became interested in automobile association work, still in its infancy, and became executive secretary of the Toledo Automobile Club, a position he held until his death in 1937.

Dr. McCormick, who has a brother in the public relations field and a sister married to a faculty member of St. Louis University, obtained his B.A. and M.A. degrees from St. John's University, Toledo, in 1911 and 1913, respectively. He acquired his medical degree in 1915 at St. Louis University, where he also established himself as a star forward on the basketball team, manager of the football team for one year and an active participant in several other extracurricular activities, including dramatics. Family historians record he did so well as an amateur actor in later years that he once got an offer from a Hollywood studio for a screen test. In turning down this chance of a lifetime, he explained to friends: "I'm afraid I would be the only man in Hollywood with just one wife and six kids."

Although he was 24 when he began his internship at St. Vincent's Hospital, Dr. McCormick didn't get rolling as a private practitioner until five years later because of a problem similar to one being faced by so many young medical graduates today—military service. Early in 1917 he enlisted in the Army's Medical Corps Reserve. In August of that year, just a few months after he had gone into private medical practice, he was called into the Army and assigned immediately to overseas duty with the British Expeditionary Forces. He served throughout the war with the 47th North Midland British Division, which broke the Hindenburg Line. Promoted from lieutenant to major, he was awarded the British Military Cross and given a dinner by his comrades upon his recall to the U. S. forces. After returning to this country, he served for a few months at Walter Reed Hospital before his discharge in 1919. He resumed practice in Toledo the following year in association with Dr. Frederick M. Douglass, with whom he worked for eight years. After the war, Dr. McCormick took an active interest in veterans' affairs and is a past commander of the American Legion's Frank Terneau Post. He is now a member of Toledo Post and the 40 and 8.

A close friend said recently: "Some people think the doctor is overtaxing his energy with his nonprofessional activities. However, I know he feels deeply that all of this work is just as much a contribution to the medical profession as anything he does in his regular practice. He feels keenly about the need for doctors to be active in community affairs."

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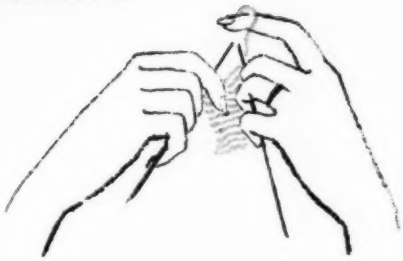

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► 1953 MEDICAL PROGRESS

Edited by Morris Fishbein, M.D. 301 pages. 1953, The Blakiston Company, New York & Toronto. $5.00.

The ever increasing number of papers and of new journals devoted to current medical literature makes it virtually impossible for anyone to keep abreast the latest developments in medicine. Dr. Fishbein, with the assistance of 24 authors reporting on the advances in 16 special fields, makes it possible for any practicing physician to have the latest knowledge and judgment of these skilled specialists. All of the recent innovations of importance and some items of current interest to the doctor in meeting his daily problems will be found in this book.

The introductory chapter on heart disease by Dr. Paul White is a complete statement of the problems encountered in practice and the recent additions to our knowledge in this field. It is a thoughtful analysis of past methods and noteworthy advances that merits close reading and study.

Major medical subjects are covered in the chapters on rheumatic diseases, arterial hypertension, infectious diseases and allergy in which the more current items of therapy as the newer antibiotics, APRESOLINE®, hexamethonium, hydrocortisone (Compound F) and antihistaminics are discussed. Diseases of the chest and gastrointestinal problems are reviewed quite comprehensively. The chapter by Dr. Paul Wermer includes discussions on probenecid (benemid), a uremicemic agent; nallene hydrochloride, an agent that reverses the respiratory depression caused by morphine; isonicotinic agents, so useful in the treatment of tuberculosis; apresoline, a drug that has a place in the control of hypertension; NEOHYDRIN®, the recently developed oral mercurial diuretic, and primaquine, the safe and effective drug for the control and treatment of malaria. A chapter on nutrition gives a brief account of some of the methods used in research and the practical clinical applications.

The sections on general surgery, urology, obstetrics, ear, nose and throat, and orthopedic surgery are analytic evaluations of the more important papers that appeared during the year and contain much significant technical information. The discussions on dermatology by Dr. Herbert Rattner and on psychiatry and psychosomatic medicine by Dr. Francis Braceland are especially well written.

H. C. L.

► NEUROSURGERY IN GENERAL PRACTICE

By Adrien ver Brugghen, M.B., Clinical Professor of Neurological Surgery (Rush), University of Illinois College of Medicine, Chicago. 665 pages with 282 figures. 1952, Charles C Thomas, Springfield, Illinois. $14.00.

Dr. ver Brugghen has admirably accomplished his purpose of acquainting physicians doing general practice with the clinical problems encountered in neurologic surgery.

The first section of the book concerns trauma to the head and spine. Typical of the material covered are answers to questions such as how to detect the development of an extradural hematoma or what therapy should be instituted by the general practitioner for a patient with a compound depressed skull fracture.

In the second part of the book Dr. ver Brugghen discusses the diagnosis and therapy of tumors of the brain and spinal cord. The differential diagnosis between these and lesions such

(Continued on page A-56)

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as subacute combined degeneration, multiple sclerosis and others is emphasized.

The remainder and major portion of the book is a discussion of the surgical treatment of hypertension, herniated intervertebral disks, relief of pain, and infections of the central nervous system. These chapters are brief, sometimes too brief to permit an adequate understanding of the lesion. This is unfortunate for it could tend to confuse the reader. The opinions presented are entirely those of Dr. ver Brugghen. The bibliography which is inserted after each chapter is sparse and not particularly up to date.

There is nothing particularly new presented in this book; however, that is not the author's stated purpose. Rather it is to inform the general practitioner how better to recognize neurologic lesions, what preliminary and possibly definitive therapy can be instituted by him, and what can be expected relative to prognosis. He gives very practical advice on the measures such physicians should undertake personally. It is a teaching book for easy reference by these physicians.

L. A. F.

► THE 1952 YEAR BOOK OF PEDIATRICS

Edited by Sydney S. Gellis, M.D., Assistant Professor of Pediatrics, Harvard Medical School. 423 pages with 112 figures. 1952, The Year Book Publishers, Chicago. $5.50.

For 46 years Dr. Isaac Abt compiled and abstracted the most important contributions in pediatric research; Dr. Sydney Gellis, assistant professor of pediatrics, Harvard Medical School, is the present editor of this Year Book.

It is impossible to review all or even a large number of the articles abstracted. The best a reviewer can do is to select but a couple of the 17 chapters which he believes to be of the most practical importance to the practicing physician.

It is now about five years since the "miracle" hormones ACTH and cortisone were offered for practical use. Although dramatic results have been recorded in several diseases the last word has not yet been said. For example, there is still considerable controversy as to their value and indications in rheumatic fever and its complications. The majority of the investigators report that these hormones cause rapid disappearance of fever and polyarthritis and general improvement of the patient. However, after discontinuance of therapy there persists evidence of rheumatic activity. What has been said of rheumatic fever can also be said of rheumatoid arthritis and Still's disease.

One of the most significant studies on the antibiotics is "Prevention of rheumatic fever by the use of depot penicillin in preceding streptococcic infections of the throat" (p. 224). Wannamaker, et al. showed that early treatment of streptococcic respiratory infections with penicillin, especially in exudative tonsillitis, significantly decreased the incidence of rheumatic fever and its associated heart disease. AUREOMYCIN® also reduces the incidence of rheumatic fever but is not as effective in reducing the carrier incidence. A 14 to 1 contrast in the incidence of rheumatic fever in favor of the treated group places a serious responsibility on the attending physician to help eliminate this crippling disease by making early, more sharply defined diagnoses.

In answer to the request by the Editor for suggestions, the reviewer would like to suggest a broader use of guest editorials to tie up the loose ends. This would help the busy practitioner make more intelligent and specific application of the conclusions reached by the contributors.

M. S.

► PHEOCHROMOCYTOMA AND THE GENERAL PRACTITIONER

By Joseph L. DeCourcy, M.D. and Cornelius B. DeCourcy, M.D. 165 pages. 1952. DeCourcy Clinic, Cincinnati.

Recent interest in pheochromocytoma makes this small volume a welcome addition to the available literature. The text offers a review of the pertinent clinical and laboratory findings in pheochromocytoma and a short historical introduction. Pathologic changes seen in the disease are summarized in a separate chapter and an explanation of the disturbed physiologic changes gives a good account of the result of overproduction of epinephrine and norepinephrine by the tumor of the adrenal glands, characteristic of pheochromocytoma.

Different types of hypertension are briefly discussed in the chapter on signs and symptoms. Although various signs and symptoms are listed in this chapter, it is regretted that the same

(Continued on page A-58)

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critical analysis is not included here or in the chapter on diagnosis and differential diagnosis. It is disappointing that the newer tests—as regitine—for pheochromocytoma and their recognized limitations are not as accurately described as was done in some of the original reports cited, such as those of Gifford, Roth and Kvale, Emlet, Grimson, Bell and Orgain and others.

The present authors have made an extensive study of the bibliography and have included frequent citations and portions of original articles to help bring the reader abreast of current literature. It is regretted, however, that the authors did not give more of their own impressions and experience rather than extensive quotations from the literature.

H. C. L.

► TEXTBOOK OF SURGERY

Edited by H. F. Moseley, M.D., Assistant Professor of Surgery, McGill University. 896 pages with 506 illustrations. 1952, C. V. Mosby Company, St. Louis. $15.00.

The combined efforts of 28 collaborators, all from McGill University and Royal Victoria Hospital of Montreal, have resulted in this new textbook of surgery. The introduction is a brief but fascinating account of the evolution of modern surgery which increases one's appreciation not only of progress today but also of various problems still unsolved in the surgical field.

There are 42 chapters, each containing a certain amount of historical consideration, followed by anatomy, physiology, pathology, physical findings, treatment and results, and a bibliography. The text is profusely illustrated, many of the color plates being reproductions of Frank Netter's work which is so well known in medical circles. All the commonly used surgical instruments are illustrated, a feature particularly suited to the student. The actual technic of surgery is illustrated in a few instances such as in splenectomy and cholecystectomy, but in others such as total gastrectomy or combined abdominal perineal resection the technic is not described. Generally accepted methods of treatment are expressed and long dissertations on controversial points avoided so that the reader will be able to grasp the subject matter without becoming confused. This is as it should be, inasmuch as this is a textbook on surgery.

No sharp distinction is made between the problem of gastric ulcer and that of duodenal ulcer, the whole topic being considered under the heading of peptic ulcer. The operative treatment of choice is stated to be a subtotal gastrectomy with the removal of three-fourths of the stomach including the pylorus (and the ulcer site in instances of duodenal ulcer). Vagotomy is discussed briefly. No statistical results are given in regard to the end results of treatment of peptic ulcer. On the treatment of carcinoma the author gives the impression that no surgery is indicated because of the high surgical mortality rate and the poor results obtained to date.

In ulcerative colitis, when medical treatment fails, it is recommended that the patient be treated vigorously with blood, antibiotics, etc. and then operated on. The surgical treatment consists of an ileostomy and subtotal colectomy. Studies showed that the mortality rate from ileostomy alone was higher than when ileostomy and subtotal colectomy were done at the same time.

This book covers adequately the various phases of the rather broad subject of general surgery. Although it is written by Canadian authors, the ideas expressed are no different from those in American literature; in fact, the majority of references to current literature are from American journals. The book has broad scope, clarity of presentation with emphasis on generalities, and systematic approach to the pathogenesis, diagnosis and treatment of disorders amenable to surgery.

Y. S.

Books received will be acknowledged in this department each month. As space permits, books of principal interest to our readers will be reviewed more extensively.

Sandoz Atlas of Haematology. By Dr. E. Undritz, Sandoz Pharmacological Research Laboratories, under the direction of Professor E. Rothlin. Translated into English by Dr. A. M. Woolman. Printed by Frobenius Ltd., Basel, Switzerland, 1952.

Comroe's Arthritis and Allied Conditions. Completely revised and rewritten. Edited by Joseph Lee Hollander, M.D., Associate Professor of Medicine and Chief of Division of Rheumatology, Graduate School of Medicine, University of Pennsylvania, Philadelphia. With 17 Collaborating Editors. Ed. 5. 1,103 pages with 399 illustrations. 1953, Lea & Febiger, Philadelphia. $16.00.

(Continued on page A-60)

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Snow, W. B., and Coss, J. A., N. Y. State J. Med. *52: 319, Feb. 1, 1952*

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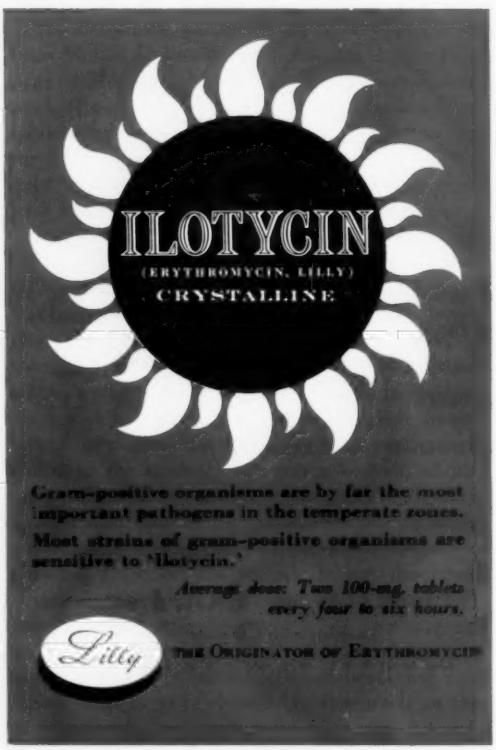
Roentgen, Radium and Radioisotope Therapy. By A. J. Delario, M.D., Head of Therapeutic Radiology, St. Joseph Hospital, Paterson, New Jersey. 371 pages with 65 illustrations and 155 tables. 1953, Lea & Febiger, Philadelphia. $7.50.

Amebiasis; Pathology, Diagnosis and Chemotherapy. By Hamilton H. Anderson, M.D., Professor and Chairman, Pharmacology and Experimental Therapeutics; Warren L. Bostick, M.D., Associate Professor of Pathology, Department of Pathology; and Herbert G. Johnstone, Ph.D., Professor of Parasitology, Parasitology and Mycology Section of the Department of Medicine, the School of Medicine, University of California Medical Center, San Francisco. 431 pages with 119 illustrations. 1953, Charles C Thomas, Springfield, Illinois. $11.50.

The Wechsler-Bellevue Scales; A Guide for Counselors. By C. H. Patterson, Veterans Administration Center, Fort Snelling, St. Paul, Minnesota. 146 pages. 1953, Charles C Thomas, Springfield, Illinois. $3.75.

Modern Treatment; A Guide for General Practice. Edited by Austin Smith, M.D., Editor, *Journal of the American Medical Association*, and Paul L. Wermer, M.D., Secretary, Committee on Research, American Medical Association. 53 authors. 1,146 pages. 1953, Paul B. Hoeber, Inc., New York, New York. $20.00.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Ocular Therapeutics. By William J. Harrison, M.D., Attending Surgeon, Wills Eye Hospital, Philadelphia, Pennsylvania. Ed. 2. 282 pages. 1953, Charles C Thomas, Springfield, Illinois.

Treatment of Respiratory Emergencies Including Bulbar Poliomyelitis. By Thomas C. Galloway, M.D., Professor Emeritus of Otolaryngology, Northwestern University Medical School, Chicago. 94 pages, illustrated. 1953, Charles C Thomas, Springfield, Illinois. $3.00.

Current Therapy 1953. Editor: Howard F. Conn, M.D. Consulting Editors: M. Edward Davis, Vincent J. Derbes, Garfield G. Duncan, Hugh J. Jewett, William J. Kerr, Perrin H. Long, H. Houston Merritt, Paul A. O'Leary, Walter L. Palmer, Hobart A. Reimann, Cyrus C. Sturgis and Robert H. Williams. 835 pages. 1953, W. B. Saunders Company, Philadelphia & London. $11.00.

How to Improve Your Sight. By Margaret Darst Corbett. Revised edition. 93 pages. 1953, Crown Publishers, Inc., New York. $1.50.

Diabetic Manual for the Doctor and Patient. By Elliott P. Joslin, M.D., Clinical Professor of Medicine, Emeritus, Harvard Medical School. Ed. 9. 315 pages with 55 figures. 1953, Lea & Febiger, Philadelphia. $3.00.

On Burns. Compiled and edited by Nathan A. Womack, M.D., Professor of Surgery, University of North Carolina School of Medicine. 191 pages with 7 illustrations. 1953, Charles C Thomas, Springfield, Illinois. $5.50.

Hypnosis in Modern Medicine. Edited by Jerome M. Schneck, M.D., Clinical Associate in Psychiatry, College of Medicine, State University of New York. 323 pages. 1953, Charles C Thomas, Springfield, Illinois. $7.50.

Stephania. By Ilona Karmel. 375 pages. 1953, Houghton Mifflin Company, Boston. $3.75.

The Management of Abdominal Operations. Edited by Rodney Maingot, F.R.C.S. 1,253 pages with 328 figures. 1953, The Macmillan Company, New York. $24.00.

Syphilitic Optic Atrophy. By Walter L. Bruetsch, M.D., Clinical Professor of Neurology and Psychiatry, Indiana University School of Medicine. 138 pages with 27 figures. 1953, Charles C Thomas, Springfield, Illinois. $5.50.

Mid-Century Psychiatry. Edited by Roy R. Grinker, M.D., Director, Institute for Psychosomatic and Psychiatric Research and Training, Michael Reese Hospital, Chicago. 183 pages. 1953, Charles C Thomas, Springfield, Illinois. $5.50.

Pain Syndromes and Their Treatment. By James M. Tarsy, M.D., Assistant Clinical Professor of Medicine, Postgraduate Medical School, New York University. 592 pages, illustrated. 1953, Charles C Thomas, Springfield, Illinois. $12.00.

An Atlas of Skull Roentgenograms. By Bernard S. Epstein, M.D., The Jewish Hospital of Brooklyn, and Leo M. Davidoff, M.D., Mount Sinai Hospital and Beth Israel Hospital, New York. 415 pages with 315 figures. 1953, Lea & Febiger, Philadelphia. $15.00.